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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	381092000721	*Total Pages*	105
First Named Inventor or Application Identifier			
Terrance P. Snutch and David L. Baillie			
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APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: **Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231**

1. [X] Fee Transmittal Form *(Submit an original, and a duplicate for fee processing)*
2. [X] Specification [*Total Pages* 26] *(preferred arrangement set forth below)*
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [X] Drawing(s) *(35 USC 113)* [*Total Sheets* 12]
4. [ ] Oath or Declaration [*Total Pages*]
   a. [ ] Newly executed (original or copy)
   b. [ ] Copy from a prior application (37 CFR 1.63(d) *(for continuation/divisional with Box 17 completed)* ***[Note Box 5 below]***
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1 33(b)
5. [ ] Incorporation By Reference *(useable if Box 4b is checked)* The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. * [ ] Microfiche Computer Program *(Appendix)*
7. * Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. [ ] Computer Readable Copy
   b. [X] Paper Copy (identical to computer copy)
   c. [X] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. [ ] Assignment Papers (cover sheet & document(s))
9. [ ] 37 CFR 3.73(b) Statement [ ] Power of Attorney *(when there is an assignee)*
10. [ ] English Translation Document *(if applicable)*
11. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
12. [ ] Preliminary Amendment
13. [X] Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
14. [X] Small Entity Statement(s) [X] Statement filed in prior application, Status still proper and desired
15. [ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. [ ] .....

17. If a CONTINUING APPLICATION, *check appropriate box and supply the requisite information:*

[X] Continuation-in-part (CIP) of prior application No: 09/346,794

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sd-7307

☒ If a paper is untimely filed in the above-referenced application by applicant or his/her representative, the Assistant Commissioner is hereby petitioned under 37 C.F.R. § 1.136(a) for the minimum extension of time required to make said paper timely. In the event a petition for extension of time is made under the provisions of this paragraph, the Assistant Commissioner is hereby requested to charge any fee required under 37 C.F.R. § 1.17(a)-(d) to **Deposit Account No. 03-1952**. However, the Assistant Commissioner is **NOT** authorized to charge the cost of the issue fee to the Deposit Account.

The filing fee has been calculated as follows:

FOR	NUMBER FILED	NUMBER EXTRA	RATE	CALCULATIONS
TOTAL CLAIMS	20 - 20 =	0	x $18.00	$0
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MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00	$260.00
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Dated: July 6, 2000

Respectfully submitted,

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Oppedahl & Larson

Applicant or Patentee: SNUTCH ET AL. Attorney's Docket No. NMED.P-001-US
Serial or Patent No.: 09/030,482 Filed or Issued: 25 February 1998
For: NOVEL HUMAN CALCIUM CHANNELS AND RELATED PROBES, CELL LINES AND METHODS

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(f) and 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am

( ) the owner of the small business concern identified below:
(X) an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN NeuroMed Technologies Inc.

ADDRESS OF CONCERN 3963 W. 24th Avenue, Vancouver, Canada V6S 1M1

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the above-captioned invention which is described in

( ) the specification filed herewith
(x) Application Serial No. 09/030,482, filed 25 February 1998.
( ) Patent No. _____, issued _____.

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e). *Note: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME _____

ADDRESS _____
( ) INDIVIDUAL ( ) SMALL BUSINESS CONCERN ( ) NONPROFIT ORGANIZATION

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I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity statu prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements ma jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Terrance P. Snutch TITLE President

ADDRESS OF PERSON SIGNING 3965 West 24th Ave, Vancouver BC V6S 1M1

SIGNATURE _____ DATE May 27, 1997

MAMMALIAN T-TYPE CALCIUM CHANNELS

This application is a continuation-in-part of application No. 09/346,794 filed 2 July 1999 which is a continuation-in-part of application No. 09/030,428 filed 25 February 1998 which claims priority from Provisional Application No. 60/039,204 filed 28 February 1997. The disclosures of these applications are incorporated by reference herein.

TECHNICAL FIELD

The invention relates to T-type calcium channel encoding sequences, expression of these sequences, and methods to screen for compounds which antagonize calcium channel activity. The invention is also related to molecular tools derived from knowledge of the molecular structure of T-type calcium channels.

BACKGROUND OF THE INVENTION

The rapid entry of calcium into cells is mediated by a class of proteins called voltage-gated calcium channels. Calcium channels are a heterogeneous class of molecules that respond to depolarization by opening a calcium-selective pore through the plasma membrane. The entry of calcium into cells mediates a wide variety of cellular and physiological responses including excitation-contraction coupling, hormone secretion and gene expression. In neurons, calcium entry directly affects membrane potential and contributes to electrical properties such as excitability, repetitive firing patterns and pacemaker activity. Miller, R.J. (1987) "Multiple calcium channels and neuronal function." *Science* 235:46-52. Calcium entry further affects neuronal functions by directly regulating calcium-dependent ion channels and modulating the activity of calcium-dependent enzymes such as protein kinase C and calmodulin-dependent protein kinase II. An increase in calcium concentration at the presynaptic nerve terminal triggers the release of neurotransmitter. Calcium entry also plays a role in neurite outgrowth and growth cone migration in developing neurons and has been implicated in long-term changes in neuronal activity.

In addition to the variety of normal physiological functions mediated by calcium channels, they are also implicated in a number of human disorders. Recently, mutations identified in human and mouse calcium channel genes have been found to account for several disorders including, familial hemiplegic migraine, episodic ataxia type 2, cerebellar ataxia, absence epilepsy and seizures. Fletcher, *et al.* (1996) "Absence epilepsy in tottering mutant mice is associated with calcium channel defects." *Cell* 87:607-617; Burgess, *et al.* (1997) "Mutation of the Ca2+ channel β subunit gene Cchb4 is associated with ataxia and seizures in the lethargic (lh) mouse." *Cell* 88:385-392; Ophoff, *et al.* (1996) "Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4." *Cell* 87:543-552; Zhuchenko, O., *et al.* (1997) "Autosomal dominant cerebellar ataxia (SCA6) associated with the small polyglutamine expansions in the α1A-voltage- dependent calcium channel." *Nature Genetics* 15:62-69.

The clinical treatment of some disorders has been aided by the development of therapeutic calcium channel antagonists. Janis, *et al.* (1991) in *Calcium Channels: Their Properties, Functions, Regulation and Clinical Relevance.* CRC Press, London.

Native calcium channels have been classified by their electrophysiological and pharmacological properties as T, L, N, P and Q types (for reviews see McCleskey, *et al.* (1991) "Functional properties of voltage-dependent calcium channels." *Curr. Topics Membr.* 39: 295-326, and Dunlap, *et al.* (1995) "Exocytotic Ca^{2+} channels in mammalian central neurons." *Trends Neurosci.* 18:89-98.). T-type (or low voltage-activated) channels describe a broad class of molecules that activate at negative potentials and are highly sensitive to changes in resting potential. The L, N, P and Q-type channels activate at more positive potentials and display diverse kinetics and voltage-dependent properties. There is some overlap in biophysical properties of the high voltage-activated channels, consequently pharmacological profiles are useful to further distinguish them. L-type channels are sensitive to dihydropyridine (DHP) agonists and antagonists, N-type channels are blocked by the *Conus geographus* peptide toxin, ω-conotoxin GVIA, and P-type channels are blocked by the peptide ω-agatoxin IVA from the venom of the funnel web spider, *Agelenopsis aperta*. A fourth type of high voltage-activated Ca channel (Q-type) has been described, although whether the Q- and P-type channels are distinct molecular entities is controversial (Sather *et al.* (1993) "Distinctive biophysical and

pharmacological properties of class A (B1) calcium channel α1 subunits." *Neuron* 11:291-303; Stea, *et al.* (1994) "Localization and functional properties of a rat brain α1A calcium channel reflect similarities to neuronal Q- and P-type channels." *Proc Natl Acad Sci (USA)* 91:10576-10580; Bourinet, E., *et al.* (1999) *Nature Neuroscience* 2:407-415). Several types of calcium conductances do not fall neatly into any of the above categories and there is variability of properties even within a category suggesting that additional calcium channels subtypes remain to be classified.

Biochemical analyses show that neuronal high-threshold calcium channels are heterooligomeric complexes consisting of three distinct subunits (α_1, $\alpha_2\delta$ and β) (reviewed by De Waard, *et al.* (1997) in *Ion Channels*, Volume 4, edited by Narahashi, T. Plenum Press, New York). The α_1 subunit is the major pore-forming subunit and contains the voltage sensor and binding sites for calcium channel antagonists. The mainly extracellular Alternatively, the α_2 subunit is disulphide-linked to the transmembrane δ subunit and both are derived from the same gene and are proteolytically cleaved *in vivo*. The β subunit is a non-glycosylated, hydrophilic protein with a high affinity of binding to a cytoplasmic region of the α_1 subunit. A fourth subunit, γ, is unique to L-type Ca channels expressed in skeletal muscle T-tubules. The isolation and characterization of γ-subunit-encoding cDNAs is described in U.S. Patent No. 5,386,025 which is incorporated herein by reference.

Molecular cloning has revealed the cDNA and corresponding amino acid sequences of six different types of α_1 subunits (α_{1A}, α_{1B}, α_{1C}, α_{1D}, α_{1E} and α_{1S}) and four types of β subunits (β_1, β_2, β_3 and β_4) (reviewed in Stea, A., Soong, T.W. and Snutch, T.P. (1994) "Voltage-gated calcium channels." in *Handbook of Receptors and Channels*. Edited by R.A. North, CRC Press). A comparison of the amino acid sequences of these α_1 subunits is included in this publication, which is incorporated herein by reference. PCT Patent Publication WO 95/04144, which is incorporated herein by reference, discloses the sequence and expression of α_{1E} calcium channel subunits.

As described in Stea, A., *et al.* (1994) (supra), the α_1 subunits are generally of the order of 2000 amino acids in length, ranging from 1873 amino acids in α_{1S} derived from rabbit to 2424 amino acids in α_{1A} derived from rabbit. Generally, these subunits contain 4 internal homologous repeats (I-IV) each having six putative alpha helical membrane

spanning segments (S1-S6) with one segment (S4) having positively charged residues every 3rd or 4th amino acid. There are a minority of a splice variant exceptions. Between domains II and III there is a cytoplasmic domain which is believed to mediate excitation-contraction coupling in α_{1S} and which ranges from 100-400 amino acid residues among the subtypes. The domains I-IV make up roughly 2/3 of the molecule and the carboxy terminus adjacent to the S6 region of domain IV is believed to be on the intracellular side of the calcium channel. There is a consensus motif (QQ-E-L-GY-WI-E) in all of the subunits cloned and described in Stea, A., *et al.* (supra) downstream from the domain I S6 transmembrane segment that is a binding site for the ß subunit.

PCT publication WO 98/38301, which describes the work of the inventors herein, and which is incorporated herein by reference, reports the first description of the molecular composition of T-type calcium channel α_1 subunits. The present application describes full-length genes for 3 mammalian subtypes, α_{1G}, α_{1H}, and α_{1I} associated with T-type calcium channels.

In some expression systems the high threshold α_1 subunits alone can form functional calcium channels although their electrophysiological and pharmacological properties can be differentially modulated by coexpression with any of the four β subunits. Until recently, the reported modulatory affects of β subunit coexpression were to mainly alter kinetic and voltage- dependent properties. More recently it has been shown that β subunits also play crucial roles in modulating channel activity by protein kinase A, protein kinase C and direct G-protein interaction. (Bourinet, *et al.* (1994) "Voltage-dependent facilitation of a neuronal α1C L-type calcium channel." *EMBO J.* 13: 5032-5039; Stea, *et al.* (1995) "Determinants of PKC- dependent modulation of a family of neuronal calcium channels." *Neuron* 15:929-940; Bourinet, *et al.* (1996) "Determinants of the G-protein-dependent opioid modulation of neuronal calcium channels." *Proc. Natl. Acad. Sci. (USA)* 93: 1486-1491.)

Because of the importance of calcium channels in cellular metabolism and human disease, it would be desirable to identify the remaining classes of α_1 subunits, and to develop expression systems for these subunits which would permit the study and characterization of these calcium channels, including the study of pharmacological modulators of calcium channel function.

DISCLOSURE OF THE INVENTION

The present invention provides sequences for a novel mammalian calcium channel subunits of T-type calcium channels, which we have labeled as α_{1G}, α_{1H} and α_{1I} subunits. Knowledge of the sequences of these calcium channel subunits may be used in the development of probes for mapping the distribution and expression of the subunits in target tissues. In addition, as the molecular structure of the α_1 subunits of these T-type calcium channels has been elucidated, it is possible to identify those portions which reside extracellularly and thus to design peptides to elicit antibodies which can be employed to assess the location and level of expression of T-type calcium channels. In addition, these subunits, either alone or assembled with other proteins, can produce functional calcium channels, which can be evaluated in model cell lines to determine the properties of the channels containing the subunits of the invention. These cell lines can be used to evaluate the effects of pharmaceuticals and/or toxic substances on calcium channels incorporating α_{1G}, α_{1H} and α_{1I} subunits. The resulting identified compounds are useful in treating conditions where undesirable T-type calcium channel activity is present. These conditions include epilepsy, sleep disorders, mood disorders, cardiac hypertrophy and arrhythmia and hypertension, among others. In addition, antisense and triplex nucleotide sequences can be designed to inhibit the production of T-type calcium channels.

In a preferred embodiment the α_1 subunits are other than those encoded by SEQ. ID. NO: 17; in another preferred embodiment the α_1 subunits are other than those encoded by sequences that include SEQ. ID. NO: 19 and SEQ. ID. NO: 21. In another preferred embodiment, probes representing portions of or all of SEQ. ID. NOS. 1-22 or 13-21 are excluded.

BRIEF DESCRIPTION OF THE DRAWINGS

Figs. 1A and B show a comparison of the waveforms and current voltage relationship for α_{1G};

Figs. 2A and B show a comparison of the waveforms and current voltage relationship for α_{1I} calcium channels.

Fig. 3 shows a comparison of the steady state inactivation profiles of the α_{1G} and α_{1I} calcium channels.

Figs. 4A-C show a comparison of the inactivation kinetics of the α_{1G} and α_{1I} calcium channels.

Figures 5A and 5B show the construction of the human α_{1G} cDNA complete sequence from partial clones.

Figure 6 shows the nucleotide and deduced amino acid sequence of human T-type calcium channel α_{1G}.

Figure 7 shows a comparison of the waveforms and current voltage relationship for human α_{1G} calcium channel.

Figure 8 shows the characteristic pore pattern for T-type channels.

MODES OF CARRYING OUT THE INVENTION

The present invention includes the following aspects for which protection is sought:

(a) novel mammalian (including human) calcium channel subunits and DNA sequences encoding such subunits. Specifically, the invention encompasses an at least partially purified DNA molecule comprising a sequence of nucleotides that encodes an α_1 subunit of a T-type calcium channel, and such α subunits *per se*. It will be appreciated that polymorphic variations may be made or may exist in the DNA of some individuals leading to minor deviations in the DNA or amino acids sequences from those shown which do not lead to any substantial alteration in the function of the calcium channel. Such variations, including variations which lead to substitutions of amino acids having similar properties are considered to be within the scope of the present invention. Thus, in one embodiment, the present application claims DNA molecules which encode α_1 subunits of mammalian T-type calcium channels, and which hybridize under conditions of medium (or higher) hybridization stringency with one or another of the specific sequences disclosed in this application. This level of hybridization stringency is generally sufficient given the length of the sequences involved to permit recovery of the subunits within the scope of the invention from mammalian DNA libraries.

Alternatively, the T-type calcium channels of the invention are recognized by their functional characteristic of low voltage gating along with defined structural characteristics which classify them as α_1 calcium channel subunits and also characterize them as of the T-type. By virtue of the present invention, these characteristics have been elucidated as follows:

One distinguishing feature of the α1G, α1H and α1I T-type channels over other types of calcium channels and sodium channels is that the pore region (P-region) in each of the four structural domains contains a diagnostic amino acid sequence implicated in channel permeability. Figure 8 shows that the T-type channels contain the residues glutamate/glutamate/aspartate/asparate (single letter amino acid code: EEDD) in the P-regions of domains I-IV. In contrast, figure 8 shows that in sodium (Na) channels the P-region of the four domains contains the residues: aspartate/glutamate/lysine/alanine (single letter amino acid code: DEKA), while high threshold calcium channels such as the L-type channel contain the residues: glutamate/glutamate/glutamate/glutamate (single letter amino acid code: EEEE). The α1G, α1H and α1I T-type channels are also distinct in this region compared to other types of ion channels including the *C. elegans* C11D2.6 and C27F2.3 and the rat NIC-channel (Figure 8).

A second distinguishing characteristic of the α_{1G}, α_{1H} and $\alpha 1_I$ T-type channels compared to other types of calcium channels is that they do not contain a β subunit binding consensus sequence in the cytoplasmic linker separating domains I and II. In contrast, all high threshold calcium channels contain a consensus sequence (single letter amino acid code: QQ-E--L-GY--WI---E) shown to physically interact with the calcium channel β subunit (Pragnell, M., De Waard, M., Mori, Y., Tanabe, T., Snutch, T.P. & Campbell, K.P., 1994, Nature 368:67-70). Thus it appears the presence of a β subunit does not modify activity, nor is its presence required.

A third distinguishing characteristic of the (α_{1G}, α_{1H} and α_{1I} T-type channels is that they do not possess an EF-hand calcium binding motif in the region carboxyl to domain IV S6. In contrast, all high threshold calcium channels contain a consensus sequence that is closely related to the EF-hand domain found in certain calcium binding

proteins (de Leon, M., Wang, Y., Jones, L., Perez-Reyes, E., Wei, X., Soong, T.W., Snutch, T.P. & Yue, D.T., 1995, Science270: 1502-1506).

Thus, as defined herein, "T-type calcium channel α_1 subunits" refers to subunits which contain these structural characteristics.

Alternatively, the T-type α_1 subunit molecules can be defined by homology to the human and rat nucleotide and amino acid sequences described herein. Thus, T-type α_1 subunits will typically have at least 50%, preferably 70% homology in terms of amino acid sequence or encoding nucleotide sequence to the sequences set forth in SEQ ID NOS. 23-28 herein or those shown in Figure 6. Preferably, the homology will be at least 80%, more preferably 90%, and most preferably 95%, 97%, 98% or 99%.

Relative homology may also be defined in terms of specific regions; as set forth above, certain regions of T-type channel α_1 subunits have very high homologies while other regions, such as the cytoplasmic region between domains II and III have less homology. Thus, T-type α_1 subunits will have over 75% homology; preferably over 85% or over 95% homology, more preferably over 98% homology in domains I-IV to those of SEQ. ID. NOS. 23-28 or Figure 6. The degree of homology in the cytoplasmic region between domains II and III may be substantially less, *e.g.*, only 25% homology, preferably, 50% homology or more preferably 60% homology. Similarly, the intracellular region downstream of domain IV may be less homologous than within domains I-IV.

(b) polynucleotide sequences useful as probes in screening human cDNA libraries for genes encoding these novel calcium channel subunits. These probes can also be used in histological assay to determine the tissue distribution of the novel calcium channel subunits.

As set forth above, the elucidation herein of the structural features of T-type subunits permits the selection of appropriate probes by selecting portions of the encoding nucleotide sequence that are particularly characteristic of this type. As set forth above, for example, T-type subunits have particular patterns of amino acids in the pore forming units as set forth in Figure 8. Alternatively, multiple probes might be used to distinguish other subunits, such as probes which represent the β-binding domain missing from the T-

type α_1 subunits combined with a probe representing a consensus sequence for calcium channel α subunits in general.

(c) at least partially purified α_1 subunits and related peptides for mammalian T-type calcium channels. These proteins and peptides can be used to generate polyclonal or monoclonal antibodies to determine the cellular and subcellular distribution of T-type calcium channel subunits.

Again, by virtue of the elucidation of the amino acid sequence of T-type α_1 subunits, it is well within the ordinary skill in the art to determine which regions of the channel are displayed extracellularly and to select these regions for the generation of antibodies.

(d) eukaryotic cell lines expressing the novel calcium channel subunits. These cell lines can be used to evaluate compounds as pharmacological modifiers of the function of the novel calcium channel subunits.

(e) a method for evaluating compounds as pharmacological modifiers of the function of the novel calcium channel subunits using the cell lines expressing those subunits alone or in combination with other calcium channel subunits.

(f) Use of the compounds identified as set forth above for the treatment of conditions which are associated with undesired calcium channel activity.

These diseases include, but are not limited to; epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, and Parkinson's disease; characterization of such associations and ultimately diagnosis of associated diseases can be carried out with probes which bind to the wild-type or defective forms of the novel calcium channels.

T-type channels in particular are responsible for rebound burst firing in central neurons and are implicated in normal brain functions such as slow-wave sleep and in neurological disorders such as epilepsy and mood disorders. They are also important in pacemaker activity in the heart, hormone secretion and fertilization, and are associated with disease states such as cardiac hypertrophy and hypertension.

As used in the specification and claims of this application, the term "T-type calcium channel" refers to a voltage-gated calcium channel having a low activation voltage, generally less than -50 mV, and most commonly less than -60 mV. T-type

calcium channels also exhibit comparatively negative steady-state inactivation properties and slow deactivation kinetics. The terms "α_1 subunit" or "α_1 calcium channel" refer to a protein subunit of a calcium channel which is responsible for pore formation and contains the voltage sensor and binding sites for calcium channel agonists and antagonists. Such subunits may be independently functional as calcium channels or may require the presence of other subunit types for complete functionality.

As used in the specification and claims of this application, the phrase "at least partially purified" refers to DNA or protein preparations in the which the specified molecule has been separated from adjacent cellular components and molecules with which it occurs in the natural state, either by virtue of performing a physical separation process or by virtue of making the DNA or protein molecule in a non-natural environment in the first place. The term encompasses cDNA molecules and expression vectors.

In accordance with the present invention, we have identified mammalian DNA sequences which code for novel T-type calcium channel α_1 subunits. These subunits are believed to represent new types of α_1 subunits of mammalian voltage-dependent calcium channels which have been designated as types α_{1G}, α_{1H} and α_{1I}.

A Bacterial Artificial Chromosome (BAC) sequence (bK206c7) was identified from sequences in Sanger Genome Sequencing Center (Cambridge, U.K.) and the Washington University Genome Sequencing Center (St. Louis. MO) that contains a nucleotide sequence encoding the α_{1I} subunit of human T-type calcium channel. The rationale for this identification is set forth in WO 98/38301, incorporated herein by reference. The relevant nucleotide sequence and the translated amino acid sequence containing 1854 amino acids are set forth in SEQ ID NOS:17 and 18.

As described in WO 98/38031, using PCR cloning techniques to identify relevant sequences within a human brain total RNA preparation, we confirmed that the novel α_{1I} calcium channel subunit is present in human brain. Subcloning of the 567 nt PCR product (SEQ. ID NO. 19, amino acids SEQ. ID NO. 20) and subsequent sequencing thereof showed that this product corresponds to the derived sequence from the bK206c7 BAC genomic sequence, the nucleotide sequence of which is given as SEQ ID NO. 17 (amino acid sequence SEQ. ID NO.18). The same experiment was performed using a rat

brain RNA preparation and resulted in recovery of a substantially identical PCR product. (SEQ ID. NO. 21). The protein encoded by the rat PCR product (SEQ ID NO. 22) is 96% identical to the human PCR product (SEQ. ID NO. 20).

These sequences, which encode a partial subunit were used as a basis for constructing full length human or rat α_{1I} clones. Briefly, the subcloned α_{1I} PCR product is radiolabeled by random hexamer priming according to standard methods (See, Sambrook , J., Fritsch, E.F. and Maniatis, T. (1989) *Molecular Cloning, A Laboratory Manual*. Cold Spring Harbor Press) and used to screen commercial human brain cDNA libraries (Stratagene, La Jolla, CA). The screening of cDNA libraries follows standard methods and includes such protocols as infecting bacteria with recombinant lambda phage, immobilizing lambda DNA to nitrocellulose filters and screening under medium hybridization stringency conditions with radiolabeled probe. cDNA clones homologous to the probe are identified by autoradiography. Positive clones are purified by sequential rounds of screening.

Following this protocol, most purified cDNA's are likely to be partial sequence clones due the nature of the cDNA library synthesis. Full length clones are constructed from cDNA's which overlap in DNA sequence. Restriction enzyme sites which overlap between cDNAs are used to ligate the individual cDNA's to generate a full-length cDNA. For subsequent heterologous expression, the full-length cDNA is subcloned directly into an appropriate vertebrate expression vector, such as pcDNA-3 (Invitrogen, San Diego, CA) in which expression of the cDNA is under the control of a promoter such as the CMV major intermediate early promoter/enhancer. Other suitable expression vectors include, for example, pMT2, pRC/CMV, pcDNA3.1 and pCEP4.

Following these protocols, full length mammalian α_{1G}, α_{1H} and α_{1I} calcium channel subunit cDNAs were isolated by using the 567 base pair human fragment (SEQ. ID NO. 19) to screen a rat brain cDNA library. Sequencing of the recovered sequences identified the three distinct classes of calcium channel subunits which have been denominated herein as α_{1G}, α_{1H} and α_{1I} subunits. For each class of subunit, complete sequencing of the largest cDNA confirmed that it represented only a portion of the predicted calcium channel coding region. Complete sequences for the three new subunits were obtained by rescreening the rat brain cDNA library with probes derived from the

partial length cDNAs to obtain overlapping segments. These segments were combined to form a complete gene by restriction digestion and ligation. The complete cDNA sequences of the rat α_{1G}, α_{1H} and α_{1I} subunits are given by SEQ. ID NOS. 23, 25 and 27, respectively. Corresponding amino acid sequences are given by SEQ. ID NOS. 24, 26 and 28. The same techniques are employed to recover human sequences by screening of a human or other mammalian library. Thus, for example, partial length human sequences for α_{1G} and α_{1H} T- type calcium channels have been recovered using the same probe (SEQ. ID NO. 19) and the full length rat α_{1I} cDNA (SEQ. ID. NO. 27) has been used to recover a partial length DNA encoding a human α_{1I} T-type calcium channel. The DNA and amino acid sequences for these partial length human calcium channels are given by SEQ. ID NOS. 30-35. A complete coding sequence for human α_{1G} was also obtained and is set forth, along with the deduced amino acid reference, in Figure 6.

Once the full length cDNA is cloned into an expression vector, the vector is then transfected into a host cell for expression. Suitable host cells include *Xenopus* oocytes or mammalian cells such as human embryonic kidney cells as described in International Patent Publication No. WO 96/39512 which is incorporated herein by reference and Ltk cells as described in US Patent No. 5,386,025 which is incorporated herein by reference. Transfection into host cells may be accomplished by microinjection, lipofection, glycerol shock, electroporation calcium phosphate or particle-mediated gene transfer. The vector may also be transfected into host cells to provide coexpression of the novel α_1 subunits with other α subunits, such as an $\alpha_2\delta$ subunit or γ subunit.

To confirm that the three full length cDNAs (SEQ. ID NOS. 23, 25 and 27) encoded functional calcium channels, the α_{1G} and α_{1I} cDNAs were transiently transfected into human embryonic kidney cells and evaluated using electrophysiological recording techniques. The results are consistent with a role of these subunits in native T-type channels in nerve, muscle and endocrine cells. Similarly, a full length clone encoding human α_{1G} T-type subunit was recovered and verified to have the characteristic properties of T-type channels.

The resulting cell lines expressing functional calcium channels including the novel α_1 subunits of the invention can be used test compounds for pharmacological activity with respect to these calcium channels. Thus, the cell lines are useful for

screening compounds for pharmaceutical utility. Such screening can be carried out using several available methods for evaluation of the interaction, if any, between the test compound and the calcium channel. One such method involves the binding of radiolabeled agents that interact with the calcium channel and subsequent analysis of equilibrium binding measurements including but not limited to, on rates, off rates, K_d values and competitive binding by other molecules. Another such method involves the screening for the effects of compounds by electrophysiological assay whereby individual cells are impaled with a microelectrode and currents through the calcium channel are recorded before and after application of the compound of interest. Another method, high-throughput spectrophotometric assay, utilizes the loading the cell lines with a fluorescent dye sensitive to intracellular calcium concentration and subsequent examination of the effects of compounds on the ability of depolarization by potassium chloride or other means to alter intracellular calcium levels. Compounds to be tested as agonists or antagonists of the novel α_{1I} calcium channel subunits are combined with cells that are stably or transiently transformed with a DNA sequence encoding the α_{1G}, α_{1H} and α_{1I} calcium channel subunits of the invention and monitored using one of these techniques.

Compounds which are shown to modulate the activity of calcium channels can then be used in pharmaceutical compositions for the treatment associated with inappropriate T-type calcium channel activity. Such conditions may also include those with inappropriate calcium channel activity in general since such activity may be modified by enhancing or decreasing T-type channel activity. Conditions appropriate for such treatment include those set forth above. The compounds identified are formulated in conventional ways as set forth in Remington's "Pharmaceutical Sciences," latest edition, Mac Publishing Co., Easton, PA. Modes of administration are those appropriate for the condition to be treated and are within the ordinary skill of the practitioner.

In addition, the regulation of expression of T-type calcium channels can be achieved by constructing expression systems encoding antisense sequences or sequences designed for triplex binding to interrupt the expression of nucleotide sequences encoding the T-type calcium channels of the invention.

DNA fragments with sequences given by SEQ ID NOS. 13-17 and 19, or polynucleotides with the complete coding sequences as given by SEQ ID NOS. 23, 25

and 27 or Figure 6 or distinctive portions thereof which do not exhibit non-discriminatory levels of homology with other types of calcium channel subunits may also be used for mapping the distribution of α_{1G}, α_{1H} and α_{1I} calcium channel subunits within a tissue sample. This method follows normal histological procedures using a nucleic acid probe, and generally involves the steps of exposing the tissue to a reagent comprising a directly or indirectly detectable label coupled to a selected DNA fragment, and detecting reagent that has bound to the tissue. Suitable labels include fluorescent labels, enzyme labels, chromophores and radio-labels.

Heterologous Expression of Mammalian T-type Calcium Channels in Cells

A. Transient Transfection in Mammalian Cells

Host cells, such as human embryonic kidney cells, HEK 293 (ATCC# CRL 1573) are grown in standard DMEM medium supplemented with 2 mM glutamine and 10% fetal bovine serum. HEK 293 cells are transfected by a standard calcium-phosphate-DNA co-precipitation method using a full-length mammalian α_1 T-type calcium channel cDNA (for example, SEQ. ID. NO. 27) in a vertebrate expression vector (for example see Current protocols in Molecular Biology). The α_{1I} calcium channel cDNA may be transfected alone or in combination with other cloned subunits for mammalian calcium channels, such as $\alpha 2\delta$ and β or γ subunits, and also with clones for marker proteins such the jellyfish green fluorescent protein.

Electrophysiological Recording: After an incubation period of from 24 to 72 hrs the culture medium is removed and replaced with external recording solution (see below). Whole cell patch clamp experiments are performed using an Axopatch 200B amplifier (Axon Instruments, Burlingame, CA) linked to an IBM compatible personal computer equipped with pCLAMP software. Microelectrodes are filled with 3 M CsCl and have typical resistances from 0.5 to 2.5 Mohms. The external recording solution is 2 mM $BaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, 40 mM TEACl, 10 mM Glucose, 92 mM CsCl, (pH 7.2). The internal pipette solution is 105 mM CsCl, 25 mM TEACl, 1 mM $CaCl_2$, 11 mM EGTA, 10 mM HEPES (pH 7.2). Currents are typically elicited from a holding potential of -100 mV to various test potentials. Data are filtered at 1 kHz and recorded directly on the hard-drive of a personal computer. Leak subtraction is carried out on-line

using a standard P/5 protocol. Currents are analyzed using pCLAMP versions 5.5 and 6.0. Macroscopic current-voltage relations are fitted with the equation I = §1/(1+exp(-(V_m-V_h)/S)} x G - (V_m-E_{rev}), where V_m is the test potential, V_h is the voltage at which half of the channels are activated, and S reflects the steepness of the activation curve and is an indication of the effective gating charge movement. Inactivation curves are normalized to 1 and fitted with I = (1/1 + exp ((V_m-V_h)/S) with V_m being the holding potential. Single channel recordings are performed in the cell-attached mode with the following pipette solution (in mM): 100 $BaCl_2$, 10 HEPES, pH 7.4 and bath solution: 100 KCl, 10 EGTA, 2 $MgCl_2$, 10 HEPES, pH 7.4.

B. Transient Transfection in Xenopus Oocytes

Stage V and VI Xenopus oocytes are prepared as described by Dascal, *et al* (1986), Expression and modulation of voltage-gated calcium channels after RNA injection into Xenopus oocytes. Science 231:1147-1150. After enzymatic dissociation with collagenase, oocytes nuclei are microinjected with the human a_{1I} calcium channel cDNA expression vector construct (approximately 10 ng DNA per nucleus) using a Drummond nanoject apparatus. The α_{1I} calcium channel may be injected alone, or in combination with other mammalian calcium channel subunit cDNAs, such as the α2-δ and β1b and γ subunits. After incubation from 48 to 96 hrs macroscopic currents are recorded using a standard two microelectrode voltage-clamp (Axoclamp 2A, Axon Instruments, Burlingame, CA) in a bathing medium containing (in mM): 40 Ba(OH)2, 25 TEA-OH, 25 NaOH, 2 CsOH, 5 HEPES (pH titrated to 7.3 with methane-sulfonic acid). Pipettes of typical resistance ranging from 0.5 to 1.5 Mohms are filled with 2.8M CsCl, 0.2M CsOH, 10mM HEPES, 10mM BAPTA free acid. Endogenous Ca (and Ba) - activated Cl currents are suppressed by systematically injecting 10-30 nl of a solution containing 100mM BAPTA-free acid, 10mM HEPES (pH titrated to 7.2 with CsOH) using a third pipette connected to a pneumatic injector. Leak currents and capacitive transients are subtracted using a standard P/5 procedure.

Construction of Stable Cell Lines Expressing Mammalian T-type Calcium Channels

Mammalian cell lines stably expressing human α_{1I} calcium channels are constructed by transfecting the α_{1I} calcium channel cDNA into mammalian cells such as HEK 293 and selecting for antibiotic resistance encoded for by an expression vector. Briefly, a full-length mammalian T-type calcium channel α1 subunit cDNA (for example SEQ. ID NO. 27) subcloned into a vertebrate expression vector with a selectable marker, such as the pcDNA3 (InvitroGen, San Diego, CA), is transfected into HEK 293 cells by calcium phosphate coprecipitation or lipofection or electroporation or other method according to well known procedures (Methods in Enzymology, Volume 185, Gene Expression Technology (1990) Edited by Goeddel, D.V.). The α_{1I} calcium channel may be transfected alone, or in combination with other mammalian calcium channel subunit cDNAs, such as the α2-δ and β1b subunits, either in a similar expression vector or other type of vector using different selectable markers. After incubation for 2 days in nonselective conditions, the medium is supplemented with Geneticin (G418) at a concentration of between 600 to 800 ug/ml. After 3 to 4 weeks in this medium, cells which are resistant to G418 are visible and can be cloned as isolated colonies using standard cloning rings. After growing up each isolated colony to confluency to establish cell lines, the expression of α_{1I} calcium channels can be determined at with standard gene expression methods such as Northern blotting, RNase protection and reverse-transcriptase PCR.

The functional detection of α_{1I} calcium channels in stably transfected cells can be examined electrophysiologically, such as by whole patch clamp or single channel analysis (see above). Other means of detecting functional calcium channels include the use of radiolabeled ^{45}Ca uptake, fluorescence spectroscopy using calcium sensitive dyes such as FURA-2, and the binding or displacement of radiolabeled ligands that interact with the calcium channel.

Example 1

Partial Rat and Human Subunits

In order to recover mammalian sequences for novel calcium channels, the 567 base pair partial length human brain α_{1I} cDNA described in WO 98/3801 was gel-purified, radio-labeled with ^{32}P dATP and dCTP by random priming (Feinberg, *et al.*, 1983, *Anal. Biochem.* 132: 6-13) and used to screen a rat brain cDNA library constructed in the phase vector Lambda Zapp II. (Snutch *et al.*, 1990, *Proc Natl Acad Sci (USA)* 87: 3391-3395). Screening was carried out at 62°C in 5XSSPE (1XSSPE= 0.18 M NaCl; 1mM EDTA; 10 mM sodium phosphate, pH=7.4 0.3% SDS, 0.2 mg/ml denatured salmon sperm DNA). Filters were washed at 62°C in 0.2X SSPE/0.1% SDS. After three rounds of screening and plaque purification, positive phages were transformed into Bluescript phagemids (Stratagene, La Jolla, CA) by *in vivo* excision.

Double stranded DNA sequencing on the recombinant phagemids was performed using a modified dideoxynucleotide protocol (Biggin *et al.*, 1983, *Proc Natl Acad Sci (USA)* 80:3963-3965) and Sequenase version 2.1 (United States Biochemical Corp.). DNA sequencing identified three distinct classes of calcium channel α_1 subunits: designated as α_{1G}, α_{1H} and α_{1I} calcium channel subunits.

For each class of calcium channel α_1 subunit, the largest cDNA was completely sequenced and determined to represent only a portion of the predicted calcium channel coding region. In order to isolate the remaining portions of α_{1G} and α_{1I} calcium channel subunits, the α_{1G} clone was digested with HindIII and SpeI. The resulting 540 base pair fragment was gel purified, radiolabeled with ^{32}P dATP and dCTP by random priming and used to rescreen the rat brain cDNA library as described above. The sequence of the 540 base pair α_{1G} screening probe used is given by SEQ. ID NO. 29. Other sequences spanning regions of distinctiveness within the sequences for the subunits could also be employed.

Double-stranded DNA sequencing of the purified recombinant phagemids showed that additional α_{1G}, α_{1H} and α_{1I} calcium channel subunit cDNAs overlapped with the original partial length cDNAs and together encoded complete protein coding regions as well as portions of their respective 5' and 3' non-coding untranslated regions.

To recover further human sequences for the novel α_{1G} and α_{1H} calcium channels, the 567 base pair partial length human brain α_{1I} cDNA (SEQ. ID. NO: 19) was radio-labeled with ^{32}P dATP and dCTP by random priming and used to screen a commercial human thalamus cDNA library (Clontech). Hybridization was performed overnight at 65°C in 6 X SSPE; 0.3% SDS; 5X Denhardt's. Filters were washed at 65°C in 0.1 X SSPE/ 0.3% SDS. After four rounds of screening and plaque purification, positive phages were selected, DNA prepared and the insert cDNA excised from the lambda vector by digestion with Eco R1 restriction enzyme. The excised cDNA was subcloned into the plasmid Bluescript KS (Stratagene, La Jolla, CA) and the DNA sequence determined using a modified dideoxynucleotide protocol and Sequence version 2.1. The partial length α_{1G} cDNA isolated consisted of 2212 base pairs of which 279 base pairs were 5' noncoding and 1,933 base pairs were coding region representing 644 amino acids (SEQ. ID NOS. 30, 31). The partial α_{1H} cDNA isolated consisted of 1,608 base pairs of which 53 base pairs were 5' noncoding and 1,555 were coding region representing 518 amino acids (SEQ. ID NOS. 32, 33).

To recover further human sequences for the novel α_{1I} calcium channel, the full-length rat brain α_{1I} cDNA (SEQ. ID. NO: 27) (See Example 2) was radio-labeled ^{32}P dATP and dCTP by random priming and used to screen a commercial human hippocampus cDNA library (Stratagene). Hybridization was performed overnight at 65 °C in 6 X SSPE; 0.3% SDS; 5X Denhardt's. Filters were washed at 65 °C in 0.1 X SSPE/ 0.3% SDS. After four rounds of screening and plaque purification, positive phages were transformed into Bluescript phagemids (Stratagene, LA Jolla, CA) by *in vitro* excision. The excised cDNA DNA sequence was determined using a modified dideoxynucleotide protocol and Sequenase version 2.1. The partial α_{1I} cDNA isolated consisted of 1,080 base pairs of coding region representing 360 amino acids (SEQ. ID NOS. 34, 35).

Example 2

Full Length Rat Subunits

Double-stranded DNA sequencing of the purified recombinant phagemids from rat brain showed that additional α_{1G} and α_{1I} calcium channel cDNAs overlapped with the original partial length cDNAs and together encoded complete protein coding regions as

well as portions of their respective 5' and 3' non-coding untranslated regions. (SEQ. ID NOS. 23 and 27, respectively) In addition to the α_{1G} and α_{1I} calcium channel classes, DNA sequencing of the recombinant phagemids also identified a third class of calcium channel α_1 subunit: designated as the α_{1H} calcium channel subunit. The partial length α_{1H} calcium channel cDNAs overlapped and together encoded a complete α_{1H} coding region as well as portions of the 5' and 3' untranslated regions (SEQ. ID. NO. 25).

Electrophysiological studies were performed on transiently-transfected human embryonic kidney cells (HEK-tsa201) prepared using the general protocol above. Transfection was carried out by standard calcium phosphate precipitation. (Okayama *et al.*, 1991, *Methods in Molec. Biol.*, Vol. 7, ed. Murray, E.J.). For maintenance, HEK-tsa201 cells were cultured until approximately 70% confluent, the media removed and cells dispersed with trypsin and gentle trituration. Cells were then diluted 1:10 in culture medium (10% FBS, DMEM plus L-glutamine, pen-strp) warmed to 37°C and plated onto tissue culture dishes. For transient transfection, 0.5 mM $CaCl_2$ was mixed with a total of 20 µg of DNA (consisting of 3µg of either rat brain α_{1G} or α_{1I} calcium channel cDNA, 2 µg of CD8 plasmid marker, and 15 µg of Bluescript plasmid carrier DNA). The DNA mixture was mixed thoroughly and then slowly added dropwise to 0.5 ml of 2 times HeBS (274 mM NaCl, 20mM D-glucose, 10mM KCl, 1.4 mM Na_2HPO_4, 40 mM Hepes (pH=7.05). After incubation at room temperature for 20 min, 100 µl of the DNA mixture was slowly added to each dish of HEK-tsa201 cells and then incubated at 37°C for 24 to 48 hours in a tissue culture incubator (5% CO_2).

Positive transfectant cells were identified visually by addition of 1 μl of mouse CD8 (Lyt2) Dynabeads directly to the recording solution and gentle swirling to mix. Whole cell patch clamp readings were carried out with an Axopatch 200A amplifier (Axon Instruments) as described previously. (Zamponi *et al.*, 1997, *Nature* 385: 442-446). The external recording solution was 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, 40 mM TEA-Cl, 10 mM glucose, 92 mM CsCl, pH=7.2 with TEA-hydroxide. The internal pipette solutions was 105 mM CsCl, 25 mM TEA-Cl, 1mM $CaCl_2$, 11 mM EGTA, 10 mM HEPES, pH 7.2 with NaOH.

For determination of current-voltage (I-V) relationships, cells were held at a resting potential of -100 mV and then stepped to various depolarizing test potentials. For

steady-state inactivation, cells were held at various potentials for 20 sec. and currents recorded during a subsequent test pulse to the peak potential of the I-V. Leak currents and capacitative transients were subtracted using a P/5 procedure.

Figs. 1-4 show the results obtained for HEK cells transfected with and expressing the cDNA of sequences ID Nos. 23 and 27, which correspond to the subunits designated as α_{1G} and α_{1I}. Figs. 1A and B and 2A and B shows a comparison of the waveforms and current- voltage relationship for the two channel subunit types. In the presence of recording solution containing 2mM Ca^{2+}, both the α_{1G} and α_{1I} channel subunits exhibit activation properties consistent with native T-type calcium currents. Figs. 1A and 2A show the subunit calcium current from a cell held at -120 mV and depolarized to a series of test potentials. Figs. 1B and 2B show the magnitude of the calcium current. From a holding potential of -110 mV, both channel first activate at approximately -70 mV and peak currents are obtained between -40 and -50 mV. Upon depolarization to various test potentials, the current waveforms of the α_{1G} and α_{1I} calcium channels exhibit an overlapping pattern characteristic of native T-type channels in nerve, muscle and endocrine cells.

Fig. 3 shows steady-state inactivation profiles for the α_{1G} and α_{1I} calcium channels in HEK 293 cells transiently transformed with full length cDNAs (SEQ ID NOS. 23 or 27) for α_{1G} or α_{1I} subunits. Steady state inactivation properties were determined by stepping from -120 mV to prepulse holding potentials between -120 mV and -50 mV for 15 sec.. prior to a test potential of -30 mV. The data are plotted as normalized whole cell current versus prepulse holding potential and show that α_{1G} exhibits a V_{50} of approximately -85 mV and α_{1I} a V_{50} of approximately -93 mV. Thus, consistent with native T-type calcium channels, both of the α_{1G} and α_{1I} calcium channels exhibit pronounced steady-state inactivation at negative potentials.

Figs. 4A-C show a comparison of the voltage-dependent deactivation profiles of the α_{1G} and α_{1I} calcium channels. HEK 293 cells were transiently transfected with either an α_{1G} or α_{1I} subunit cDNA (SEQ. ID NO. 23 or 27). The deactivation properties of α_{1G} were determined by stepping from a holding potential of -100 mV to -40mV for 9 msec, and then to potentials between -120 mV and -45 mV. The deactivation properties of α_{1I} were determined by stepping from a holding potential of -100 mV to -40 mV for 20

msec, and then to potentials between -120 mV and -45 mV. Both channels exhibit slow deactivation kinetics compared to typical high-threshold channels, and is consistent with the α_{1G} and α_{1I} subunits being subunits for T-type calcium channels

Example 3

Cloning of a Full Length cDNA for the Human α1G T-Type Calcium Channel Subunit

Materials and Methods:

A full length cDNA encoding the human α_{1G} subunit was constructed from 5 overlapping clones (Figure 1B) isolated from a human thalamus cDNA library constructed in λgt11 vector (Clontech, Cat#HL5009b).s

Three λgt11 cDNA clones were isolated by conventional filter hybridization.

Clone 1 was identified by hybridization to a 567 bp cDNA probe (SEQ. ID. NO: 19) containing the transmembrane region S4 to S6 of domain I of the previously cloned human neuronal α_{1I} T-type calcium channel subunit. Clones HG10-1112 and HG5-1211 were identified by hybridization to a 1265 bp cDNA probe of the rat α_{1H} T-type calcium channel subunit spanning domain II and part of the II-III intracellular loop. cDNA probes were ^{32}P-dCTP labeled by random priming using a Multiprime DNA labeling system (Amersham Pharmacia). Plaque lifts using H-bond nylon membranes were done in duplicate following the standard protocols supplied by manufacturer (Amersham Pharmacia). Hybridization was performed for at least 16 hrs at 65°C for clone 1 and for at least 16 hrs at 58°C, clones HG10-1112 and HG5-1211. Membranes were washed in 0.1X SSC/0.3% SDS at 62°C for clone 1 and 0.2X SSC/0.1% SDS at 58°C clones HG10-1112 and HG5-1211. Blots were exposed to BioMax MS Kodak film with Kodak HE intensifying screens for at least 48 hrs at –80°C. Double positive plaques were isolated and re-screened to isolate single clones according to the procedure above. Bacteriophage DNA's were then isolated according to the λgt11 library User Manual (Clontech). Clone 1 cDNA insert was excised with EcoRI (NEB) and subcloned into pBluescriptKS (Stratagene). Clones HG10-1112 and HG5-1211 cDNA inserts were excised from λDNA with Not I (NEB) and subcloned into the Not I site of pBluescriptKS. Plasmids with cDNA inserts were transformed by electroporation into

XL-I *E. coli* host strain bacteria and sequenced using universal reverse and forward primers according to Sanger double stranded DNA sequencing method in combination with automatic sequencing ABI 100 PRISM model 377 Version 3.3 (PE Biosystems).

Clone 1 was identified as a human α_{1G} subunit containing the 5'UTR and 1933 bp of the in-frame coding region, including part of the intracellular I-II loop. Clone HG10-1112 was identified as a human α_{1G} subunit of 3915 bp, spanning DomainI (S5-S6) to the III-IV loop. Clone HG5-1211 was identified as human α_{1G} subunit of 3984 bp containing the I-II linker and C-terminus.

For expression in HEK cells, removal of 5' UTR from clone 1 was achieved by replacing 5'UTR DNA fragment flanked by Hind III/SacII restriction sites with 5'end -291 bp cDNA fragment, containing translation start site and an incorporated Hind III site for subsequent cloning into pcDNA3.1 (Invitrogen). Following PCR conditions were used: 94°C –30 sec, 45°C –30 sec, 72°C –30 sec for 5 cycles and followed by 94°C –30 sec, 48°C –30 sec, 72°C –30 sec for 20 cycles (Bio-rad Gene Cycler). The cDNA fragment was subcloned into p-Gem-T-Easy plasmid vector (Promega) and the DNA sequence determined.

The remaining region of the 3' α_{1G} subunit cDNA was obtained using the PCR method on a human thalamus cDNA library with primers MD19-sense (5'GCG TGG AGC TCT TTG GAG 3') and G26- antisense (5' GCA CCC AGT GGA GAA AGG TG 3'). The PCR protocol used was 94°C –30 sec, 58°C –30 sec, 72°C –30 sec for 25 cycles (Bio-rad Gene Cycler). A cDNA fragment of 1617 bp was subcloned into p-Gem-T-Easy plasmid vector (Promega) and sequenced. The 3'PCR cDNA was identified as a human α_{1G} subunit spanning from Domain IV-S5 to the carboxyl terminus including the stop codon.

Unique restriction sites (Figures 5A and B) of the partial cDNA clones were used to construct the full length human α_{1G} T-type calcium channel in pcDNA3.1 Zeo (+) (Invitrogen) mammalian expression vector.

The complete nucleotide and amino acid sequences are shown in Figure 6.

In order to determine the functional properties of the human α_{1G} channel standard calcium-phosphate transfection was used to transiently express the channel in HEK ts201

cells. Cells were cultured in Dulbecco's modified eagle medium (DMEM) supplemented with 10% fetal bovine serum, 200 U/ml penicillin and 0.2 mg/ml streptomycin at 37°C with 5% CO_2. At 85% confluency cells were split with 0.25% trypsin/1 mM EDTA and plated at 10% confluency on glass coverslips. At 12 hours the medium was replaced and the cells transiently transfected using a standard calcium phosphate protocol and the α_{1G} calcium channel cDNA. Fresh DMEM was supplied and the cells transferred to 28°C/5% CO_2. Cells were incubated for 1 to 2 days prior to whole cell recording. Whole cell patch recordings were performed using an Axopatch 200B amplifier (Axon Instruments) linked to an IBM compatible personal computer equipped with pCLAMP version 7.0 software. The intrapipette solution contained (in mM): 105 CsCl, 25 CsCl, 1 $CaCl_2$, 11 EGTA, 10 HEPES, pH 7.2. The extracellular solution contained (in mM): 40 TEA-Cl, 2 $CaCl_2$, 1 $MgCl_2$, 92 CsCl, 10 glucose, 10 HEPES, pH 7.2.

Figure 7 shows that the human α1G cDNA encodes a calcium channel with typical properties of a T-type current. The left panel illustrates representative current traces obtained from a holding potential of –100 mV to test pulses potentials of –90 mV to +20 mV. The traces show a typical crossover pattern and considerable inactivation during the test pulse, both of which are consistent with native T-type channels. The right panel shows a plot of the peak whole current at various test potentials and indicates that the human α1G cDNA first activates near –60 mV with maximal current near –40 mV, which is also consistent with native low-threshold T-type calcium channels.

Claims

1. A DNA molecule which comprises an expression cassette wherein said expression cassette comprises a nucleotide sequence encoding a T-type calcium channel $\acute{\alpha}_1$ subunit, said encoding sequence operably linked to control sequences to effect its expression.

2. The DNA molecule of claim 1 wherein said α_1 subunit is α_{1G}, α_{1H}, or α_{1I}.

3. The DNA molecule of claim 2 wherein said α_1 subunit is derived from a mammal.

4. Recombinant host cells modified to contain the DNA molecule of any of claims 1-3.

5. The cells of claim 4 which are mammalian cells.

6. A method to effect production of a functional calcium channel which method comprises culturing the cells of claim 4 or 5 under conditions wherein said functional calcium channels are produced.

7. A method to identify a compound which is a modulator for T-type mammalian calcium channels, which method comprises contacting the cells employed in the method of claim 6 with said compound and assessing the effect of said compound on said cells.

8. A T-type calcium channel modulator identified by the method of claim 7.

9. A method to treat conditions characterized by undesirable levels of T-type calcium channel activity which method comprises administering to a subject in need of such treatment an effective amount of the modulator of claim 8.

10. The method of claim 9 wherein said condition is cardiac hypertrophy, cardiac arrythymia, hypertension, a sleep disorder, or epilepsy.

11. A DNA molecule which comprises an expression system for a nucleotide sequence which is complementary to the nucleotide sequence encoding a T-type calcium channel α_1 subunit or which forms a triple helix with DNA comprising said encoding sequence.

12. A method to treat a condition characterized by an undesirable level of T-type calcium channel activity which method comprises administering to a subject in need of such treatment an effective amount of the DNA molecule of claim 11.

13. The method of claim 12 wherein said condition is cardiac hypertrophy, cardiac arrythmia, hypertension, a sleep disorder, or epilepsy.

14. An oligonucleotide which consists essentially of a nucleotide sequence characteristic of a T-type calcium channel α_1 subunit, said oligonucleotide coupled to or comprising a detectable label.

15. A method to map the distribution of T-type calcium channels in a tissue which method comprises contacting said tissue with the oligonucleotide of claim 14.

16. Antibodies specifically immunoreactive with the extracellular portions of a T-type calcium channel.

17. A method to map the distribution of T-type calcium channels in a tissue which method comprises contacting said tissue with the antibodies of claim 16.

ABSTRACT OF THE DISCLOSURE

Sequences and partial sequences for three types of mammalian (human and rat sequences identified) T-type calcium channel subunits which we have labeled as the α_{1G}, α_{1H} and α_{1I} subunits are provided. Knowledge of the sequence of these calcium channel permits the localization and recovery of the complete sequence from human cells, and the development of cell lines which express the novel calcium channels of the invention. These cells may be used for identifying compounds capable of acting as agonists or antagonists to the calcium channels.

α_{1G}

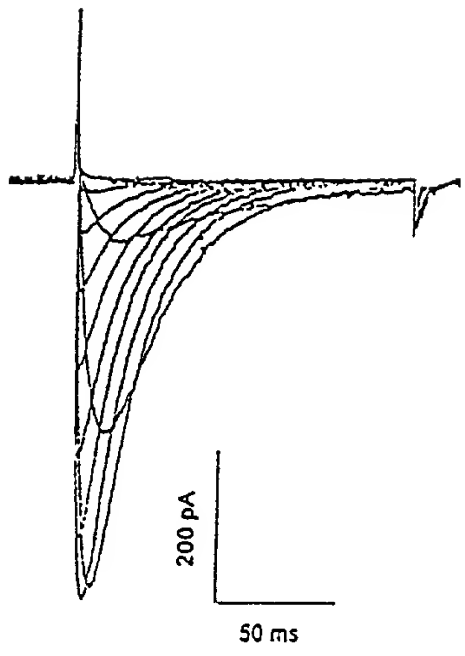


Fig. 1A

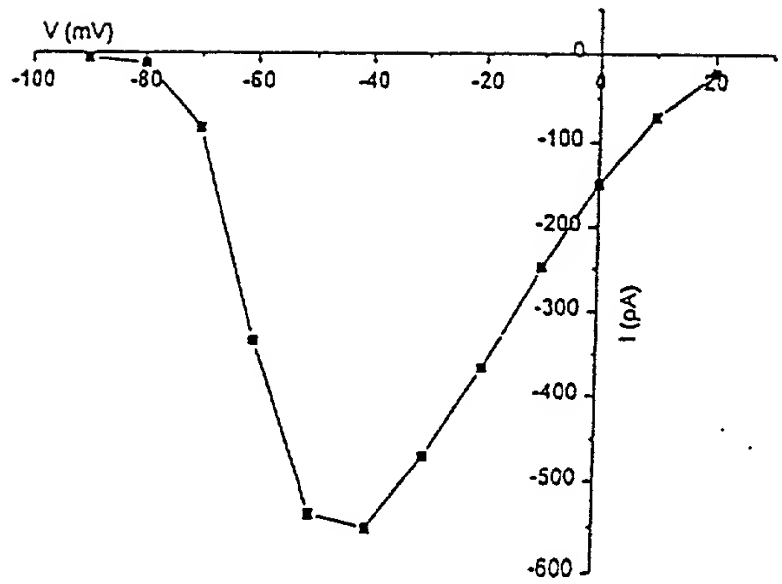


Fig. 1B

α_{1I}

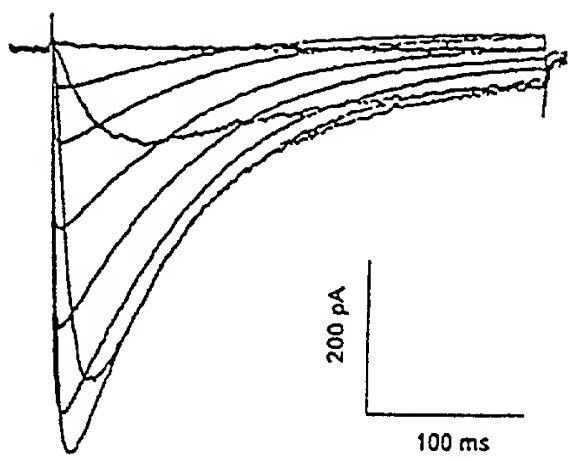


Fig. 2A

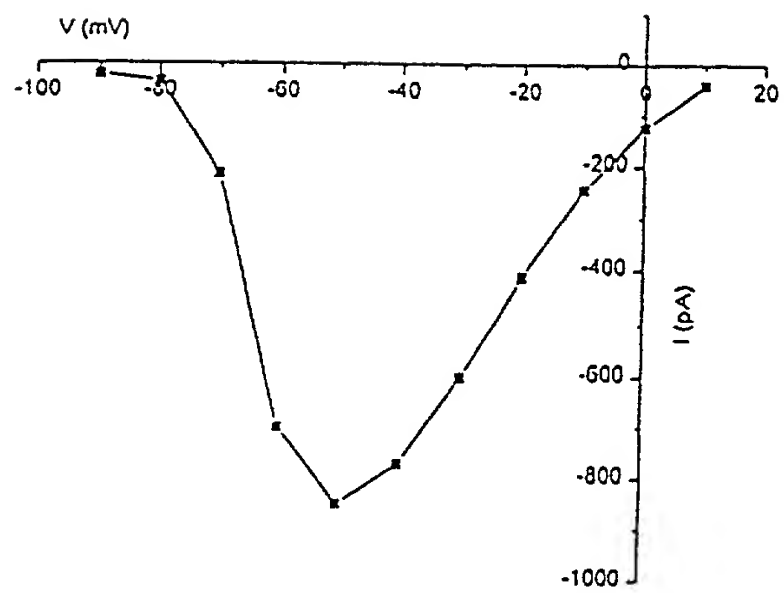


Fig. 2 B

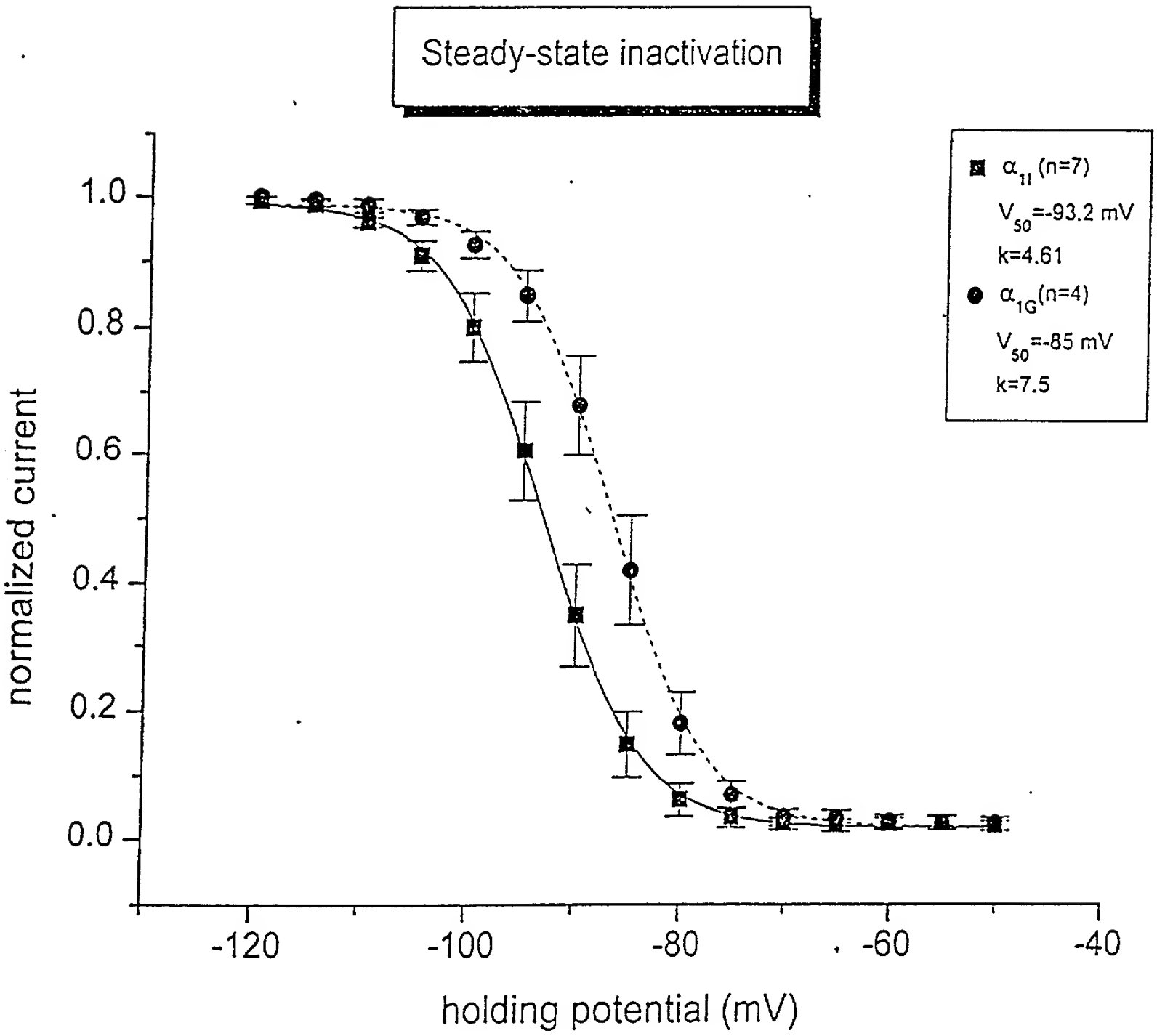

Steady-state inactivation
α_{1I} (n=7)
V_{50}=-93.2 mV
k=4.61
α_{1G}(n=4)
V_{50}=-85 mV
k=7.5
normalized current
1.0
0.8
0.6
0.4
0.2
0.0
-120
-100
-80
-60
-40
holding potential (mV)

Fig. 3

Deactivation

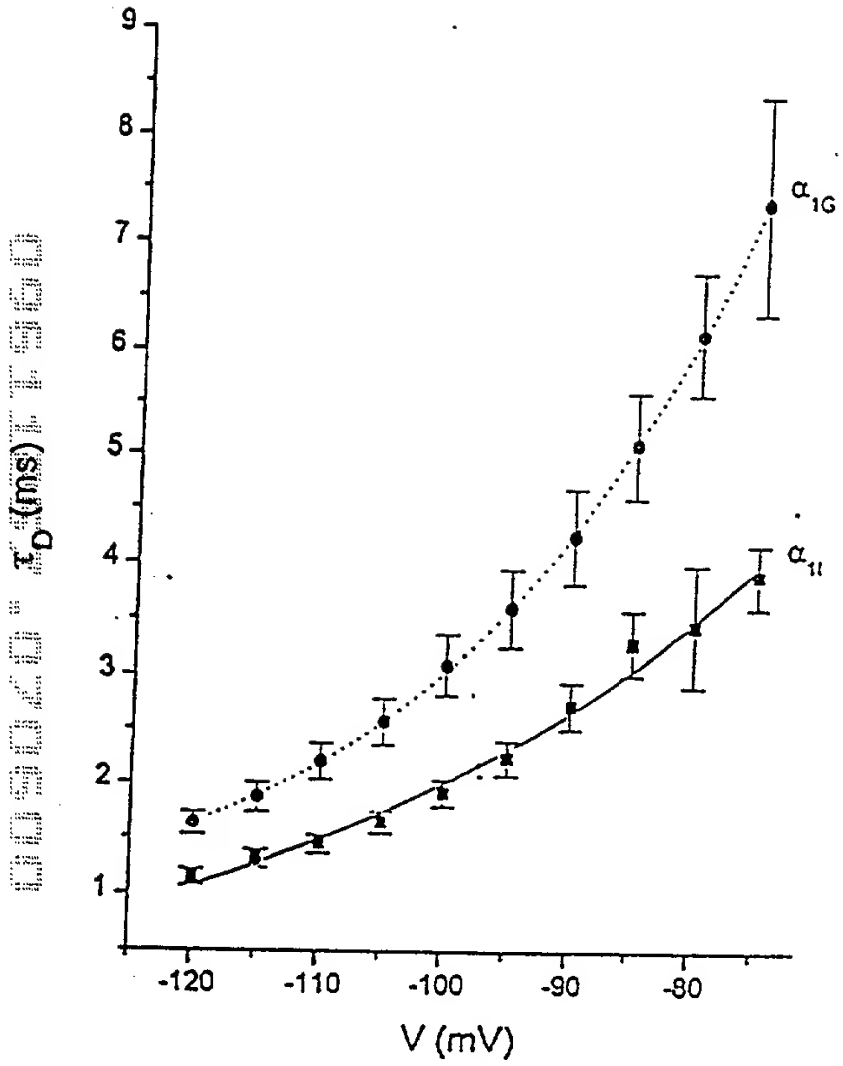
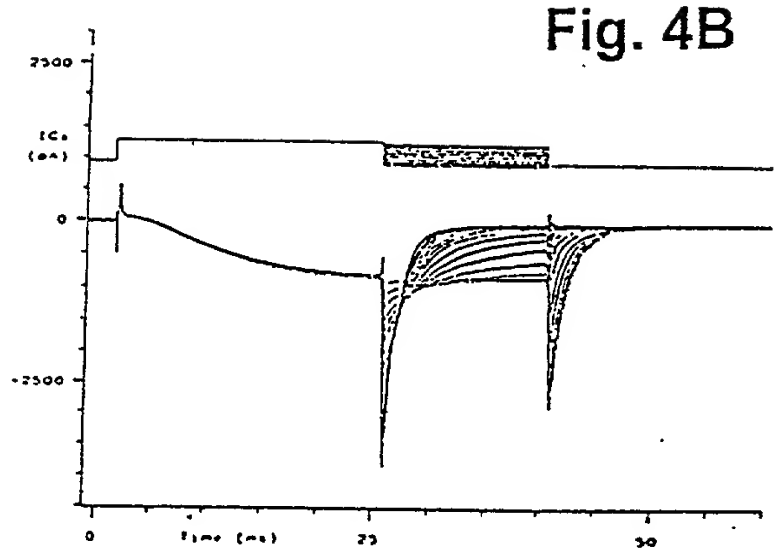


Fig. 4A

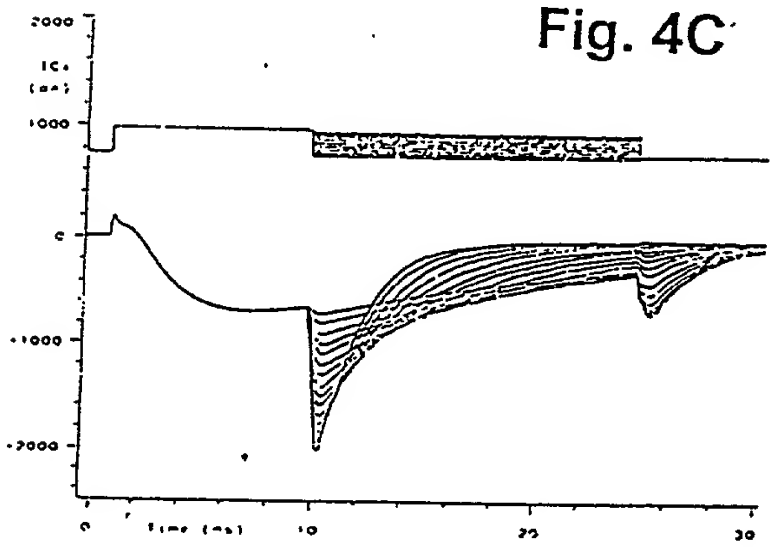
α_{1I}

Fig. 4B



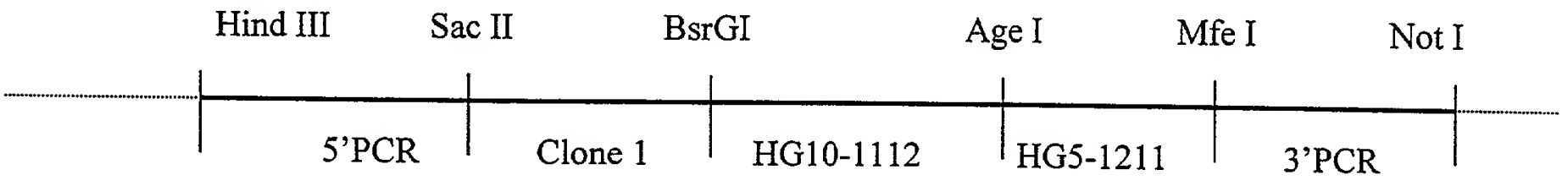
α_{1G}

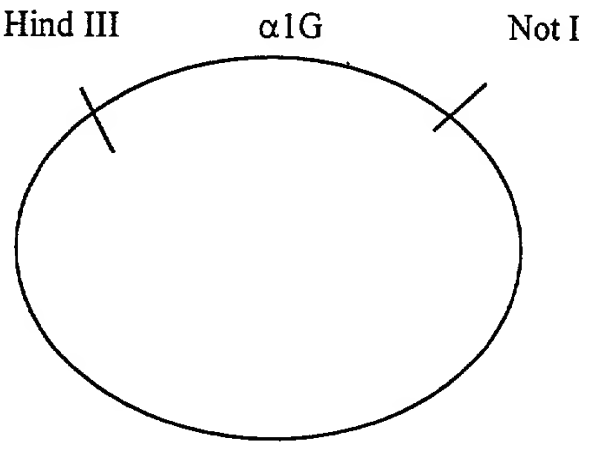
Fig. 4C



5

Figure 1A. α1G cDNA construct

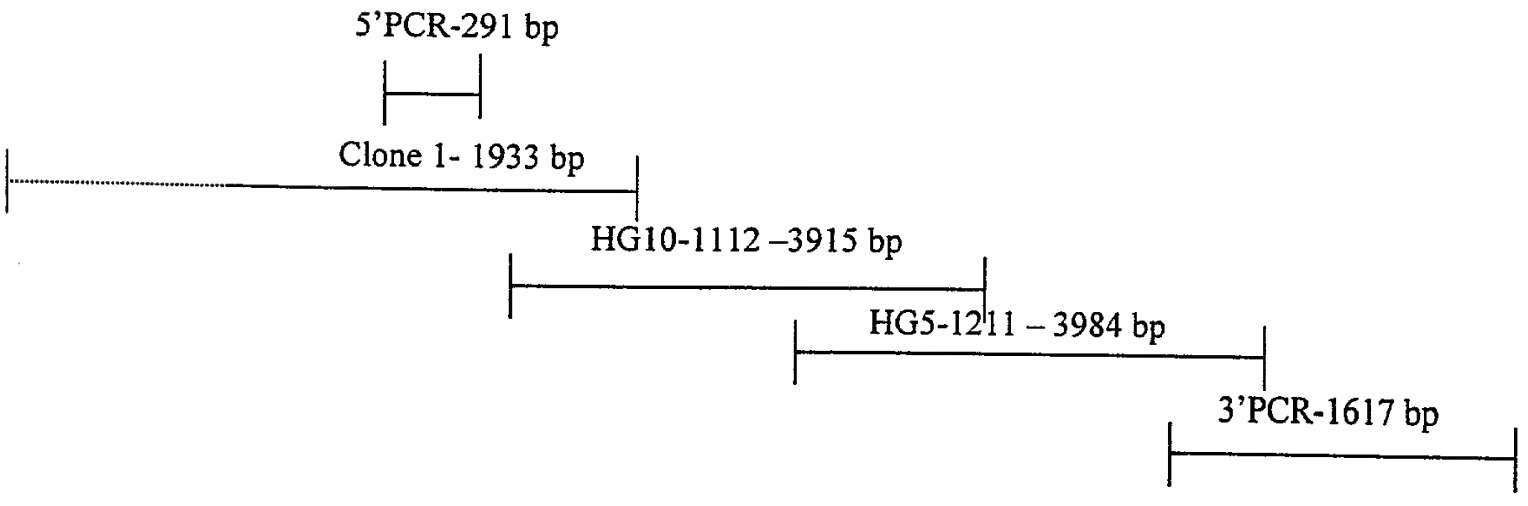




pcDNA 3.1 Zeo (+)

5

Figure 1B. α1G cDNA CLONES



Human α1 G T-type calcium channel cDNA

```
   1 aagcttgcttgcccctctccggatcgcccggggccccggctggccagagg ATG GAC GAG GAG GAG GAT GGA    71
   1                                                     M   D   E   E   E   D   G     7

  72 GCG GGC GCC GAG GAG TCG GGA CAG CCC CGG AGC TTC ATG CGG CTC AAC GAC CTG TCG GGG   131
   8 A   G   A   E   E   S   G   Q   P   R   S   F   M   R   L   N   D   L   S   G    27

 132 GCC GGG GGC CGG CCG GGG CCG GGG TCA GCA GAA AAG GAC CCG GGC AGC GCG GAC TCC GAG   191
  28 A   G   G   R   P   G   P   G   S   A   E   K   D   P   G   S   A   D   S   E    47

 192 GCG GAG GGG CTG CCG TAC CCG GCG CTG GCC CCG GTG GTT TTC TTC TAC TTG AGC CAG GAC   251
  48 A   E   G   L   P   Y   P   A   L   A   P   V   V   F   F   Y   L   S   Q   D    67

 252 AGC CGC CCG CGG AGC TGG TGT CTC CGC ACG GTC TGT AAC CCC TGG TTT GAG CGC ATC AGC   311
  68 S   R   P   R   S   W   C   L   R   T   V   C   N   P   W   F   E   R   I   S    87

 312 ATG TTG GTC ATC CTT CTC AAC TGC GTG ACC CTG GGC ATG TTC CGG CCA TGC GAG GAC ATC   371
  88 M   L   V   I   L   L   N   C   V   T   L   G   M   F   R   P   C   E   D   I   107

 372 GCC TGT GAC TCC CAG CGC TGC CGG ATC CTG CAG GCC TTT GAT GAC TTC ATC TTT GCC TTC   431
 108 A   C   D   S   Q   R   C   R   I   L   Q   A   F   D   D   F   I   F   A   F   127

 432 TTT GCC GTG GAG ATG GTG GTG AAG ATG GTG GCC TTG GGC ATC TTT GGG AAA AAG TGT TAC   491
 128 F   A   V   E   M   V   V   K   M   V   A   L   G   I   F   G   K   K   C   Y   147

 492 CTG GGA GAC ACT TGG AAC CGG CTT GAC TTT TTC ATC GTC ATC GCA GGG ATG CTG GAG TAC   551
 148 L   G   D   T   W   N   R   L   D   F   F   I   V   I   A   G   M   L   E   Y   167

 552 TCG CTG GAC CTG CAG AAC GTC AGC TTC TCA GCT GTC AGG ACA GTC CGT GTG CTG CGA CCG   611
 168 S   L   D   L   Q   N   V   S   F   S   A   V   R   T   V   R   V   L   R   P   187

 612 CTC AGG GCC ATT AAC CGG GTG CCC AGC ATG CGC ATC CTT GTC ACG TTG CTG CTG GAT ACG   671
 188 L   R   A   I   N   R   V   P   S   M   R   I   L   V   T   L   L   L   D   T   207

 672 CTG CCC ATG CTG GGC AAC GTC CTG CTG CTC TGC TTC TTC GTC TTC TTC ATC TTC GGC ATC   731
 208 L   P   M   L   G   N   V   L   L   L   C   F   F   V   F   F   I   F   G   I   227

 732 GTC GGC GTC CAG CTG TGG GCA GGG CTG CTT CGG AAC CGA TGC TTC CTA CCT GAG AAT TTC   791
 228 V   G   V   Q   L   W   A   G   L   L   R   N   R   C   F   L   P   E   N   F   247

 792 AGC CTC CCC CTG AGC GTG GAC CTG GAG CGC TAT TAC CAG ACA GAG AAC GAG GAT GAG AGC   851
 248 S   L   P   L   S   V   D   L   E   R   Y   Y   Q   T   E   N   E   D   E   S   267

 852 CCC TTC ATC TGC TCC CAG CCA CGC GAG AAC GGC ATG CGG TCC TGC AGA AGC GTG CCC ACG   911
 268 P   F   I   C   S   Q   P   R   E   N   G   M   R   S   C   R   S   V   P   T   287

 912 CTG CGC GGG GAC GGG GGC GGT GGC CCA CCT TGC GGT CTG GAC TAT GAG GCC TAC AAC AGC   971
 288 L   R   G   D   G   G   G   G   P   P   C   G   L   D   Y   E   A   Y   N   S   307

 972 TCC AGC AAC ACC ACC TGT GTC AAC TGG AAC CAG TAC TAC ACC AAC TGC TCA GCG GGG GAG  1031
 308 S   S   N   T   T   C   V   N   W   N   Q   Y   Y   T   N   C   S   A   G   E   327

1032 CAC AAC CCC TTC AAG GGC GCC ATC AAC TTT GAC AAC ATT GGC TAT GCC TGG ATC GCC ATC  1091
 328 H   N   P   F   K   G   A   I   N   F   D   N   I   G   Y   A   W   I   A   I   347

1092 TTC CAG GTC ATC ACG CTG GAG GGC TGG GTC GAC ATC ATG TAC TTT GTG ATG GAT GCT CAT  1151
 348 F   Q   V   I   T   L   E   G   W   V   D   I   M   Y   F   V   M   D   A   H   367

1152 TCC TTC TAC AAT TTC ATC TAC TTC ATC CTC CTC ATC ATC GTG GGC TCC TTC TTC ATG ATC  1211
 368 S   F   Y   N   F   I   Y   F   I   L   L   I   I   V   G   S   F   F   M   I   387

1212 AAC CTG TGC CTG GTG GTG ATT GCC ACG CAG TTC TCA GAG ACC AAG CAG CGG GAA AGC CAG  1271
 388 N   L   C   L   V   V   I   A   T   Q   F   S   E   T   K   Q   R   E   S   Q   407

1272 CTG ATG CGG GAG CAG CGT GTG CGG TTC CTG TCC AAC GCC AGC ACC CTG GCT AGC TTC TCT  1331
 408 L   M   R   E   Q   R   V   R   F   L   S   N   A   S   T   L   A   S   F   S   427

1332 GAG CCC GGC AGC TGC TAT GAG GAG CTG CTC AAG TAC CTG GTG TAC ATC CTT CGT AAG GCA  1391
 428 E   P   G   S   C   Y   E   E   L   L   K   Y   L   V   Y   I   L   R   K   A   447
```

Figure 6

sd-7045

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1392 GCC CGC AGG CTG GCT CAG GTC TCT CGG GCA GCA GGT GTG CGG GTT GGG CTG CTC AGC AGC  1451
 448 A   R   R   L   A   Q   V   S   R   A   A   G   V   R   V   G   L   L   S   S    467

1452 CCA GCA CCC CTC GGG GGC CAG GAG ACC CAG CCC AGC AGC AGC TGC TCT CGC TCC CAC CGC  1511
 468 P   A   P   L   G   G   Q   E   T   Q   P   S   S   S   C   S   R   S   H   R    487

1512 CGC CTA TCC GTC CAC CAC CTG GTG CAC CAC CAC CAC CAC CAT CAC CAC CAC TAC CAC CTG  1571
 488 R   L   S   V   H   H   L   V   H   H   H   H   H   H   H   H   H   Y   H   L    507

1572 GGC AAT GGG ACG CTC AGG GCC CCC CGG GCC AGC CCG GAG ATC CAG GAC AGG GAT GCC AAT  1631
 508 G   N   G   T   L   R   A   P   R   A   S   P   E   I   Q   D   R   D   A   N    527

1632 GGG TCC CGC AGG CTC ATG CTG CCA CCA CCC TCG ACG CCT GCC CTC TCC GGG GCC CCC CCT  1691
 528 G   S   R   R   L   M   L   P   P   P   S   T   P   A   L   S   G   A   P   P    547

1692 GGT GGC GCA GAG TCT GTG CAC AGC TTC TAC CAT GCC GAC TGC CAC TTA GAG CCA GTC CGC  1751
 548 G   G   A   E   S   V   H   S   F   Y   H   A   D   C   H   L   E   P   V   R    567

1752 TGC CAG GCG CCC CCT CCC AGG TCC CCA TCT GAG GCA TCC GGC AGG ACT GTG GGC AGC GGG  1811
 568 C   Q   A   P   P   P   R   S   P   S   E   A   S   G   R   T   V   G   S   G    587

1812 AAG GTG TAT CCC ACC GTG CAC ACC AGC CCT CCA CCG GAG ACG CTG AAG GAG AAG GCA CTA  1871
 588 K   V   Y   P   T   V   H   T   S   P   P   P   E   T   L   K   E   K   A   L    607

1872 GTA GAG GTG GCT GCC AGC TCT GGG CCC CCA ACC CTC ACC AGC CTC AAC ATC CCA CCC GGG  1931
 608 V   E   V   A   A   S   S   G   P   P   T   L   T   S   L   N   I   P   P   G    627

1932 CCC TAC AGC TCC ATG CAC AAG CTG CTG GAG ACA CAG AGT ACA GGT GCC TGC CAA AGC TCT  1991
 628 P   Y   S   S   M   H   K   L   L   E   T   Q   S   T   G   A   C   Q   S   S    647

1992 TGC AAG ATC TCC AGC CCT TGC TTG AAA GCA GAC AGT GGA GCC TGT GGT CCA GAC AGC TGC  2051
 648 C   K   I   S   S   P   C   L   K   A   D   S   G   A   C   G   P   D   S   C    667

2052 CCC TAC TGT GCC CGG GCC GGG GCA GGG GAG GTG GAG CTC GCC GAC CGT GAA ATG CCT GAC  2111
 668 P   Y   C   A   R   A   G   A   G   E   V   E   L   A   D   R   E   M   P   D    687

2112 TCA GAC AGC GAG GCA GTT TAT GAG TTC ACA CAG GAT GCC CAG CAC AGC GAC CTC CGG GAC  2171
 688 S   D   S   E   A   V   Y   E   F   T   Q   D   A   Q   H   S   D   L   R   D    707

2172 CCC CAC AGC CGG CGG CAA CGG AGC CTG GGC CCA GAT GCA GAG CCC AGC TCT GTG CTG GCC  2231
 708 P   H   S   R   R   Q   R   S   L   G   P   D   A   E   P   S   S   V   L   A    727

2232 TTC TGG AGG CTA ATC TGT GAC ACC TTC CGA AAG ATT GTG GAC AGC AAG TAC TTT GGC CGG  2291
 728 F   W   R   L   I   C   D   T   F   R   K   I   V   D   S   K   Y   F   G   R    747

2292 GGA ATC ATG ATC GCC ATC CTG GTC AAC ACA CTC AGC ATG GGC ATC GAA TAC CAC GAG CAG  2351
 748 G   I   M   I   A   I   L   V   N   T   L   S   M   G   I   E   Y   H   E   Q    767

2352 CCC GAG GAG CTT ACC AAC GCC CTA GAA ATC AGC AAC ATC GTC TTC ACC AGC CTC TTT GCC  2411
 768 P   E   E   L   T   N   A   L   E   I   S   N   I   V   F   T   S   L   F   A    787

2412 CTG GAG ATG CTG CTG AAG CTG CTT GTG TAT GGT CCC TTT GGC TAC ATC AAG AAT CCC TAC  2471
 788 L   E   M   L   L   K   L   L   V   Y   G   P   F   G   Y   I   K   N   P   Y    807

2472 AAC ATC TTC GAT GGT GTC ATT GTG GTC ATC AGC GTG TGG GAG ATC GTG GGC CAG CAG GGG  2531
 808 N   I   F   D   G   V   I   V   V   I   S   V   W   E   I   V   G   Q   Q   G    827

2532 GGC GGC CTG TCG GTG CTG CGG ACC TTC CGC CTG ATG CGT GTG CTG AAG CTG GTG CGC TTC  2591
 828 G   G   L   S   V   L   R   T   F   R   L   M   R   V   L   K   L   V   R   F    847

2592 CTG CCG GCG CTG CAG CGG CAG CTG GTG GTG CTC ATG AAG ACC ATG GAC AAC GTG GCC ACC  2651
 848 L   P   A   L   Q   R   Q   L   V   V   L   M   K   T   M   D   N   V   A   T    867

2652 TTC TGC ATG CTG CTT ATG CTC TTC ATC TTC ATC TTC AGC ATC CTG GGC ATG CAT CTC TTC  2711
 868 F   C   M   L   L   M   L   F   I   F   I   F   S   I   L   G   M   H   L   F    887

2712 GGC TGC AAG TTT GCC TCT GAG CGG GAT GGG GAC ACC CTG CCA GAC CGG AAG AAT TTT GAC  2771
 888 G   C   K   F   A   S   E   R   D   G   D   T   L   P   D   R   K   N   F   D    907

2772 TCC TTG CTC TGG GCC ATC GTC ACT GTC TTT CAG ATC CTG ACC CAG GAG GAC TGG AAC AAA  2831
 908 S   L   L   W   A   I   V   T   V   F   Q   I   L   T   Q   E   D   W   N   K    927

2832 GTC CTC TAC AAT GGT ATG GCC TCC ACG TCG TCC TGG GCG GCC CTT TAT TTC ATT GCC CTC  2891
 928 V   L   Y   N   G   M   A   S   T   S   S   W   A   A   L   Y   F   I   A   L    947

2892 ATG ACC TTC GGC AAC TAC GTG CTC TTC AAT TTG CTG GTC GCC ATT CTG GTG GAG GGC TTC  2951
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 948 M   T   F   G   N   Y   V   L   F   N   L   L   V   A   I   L   V   E   G   F   967

2952 CAG GCG GAG GAA ATC AGC AAA CGG GAA GAT GCG AGT GGA CAG TTA AGC TGT ATT CAG CTG 3011
 968 Q   A   E   E   I   S   K   R   E   D   A   S   G   Q   L   S   C   I   Q   L   987

3012 CCT GTC GAC TCC CAG GGG GGA GAT GCC AAC AAG TCC GAA TCA GAG CCC GAT TTC TTC TCA 3071
 988 P   V   D   S   Q   G   G   D   A   N   K   S   E   S   E   P   D   F   F   S  1007

3072 CCC AGC CTG GAT GGT GAT GGG GAC AGG AAG AAG TGC TTG GCC TTG GTG TCC CTG GGA GAG 3131
1008 P   S   L   D   G   D   G   D   R   K   K   C   L   A   L   V   S   L   G   E  1027

3132 CAC CCG GAG CTG CGG AAG AGC CTG CTG CCG CCT CTC ATC ATC CAC ACG GCC GCC ACA CCC 3191
1028 H   P   E   L   R   K   S   L   L   P   P   L   I   I   H   T   A   A   T   P  1047

3192 ATG TCG CTG CCC AAG AGC ACC AGC ACG GGC CTG GGC GAG GCG CTG GGC CCT GCG TCG CGC 3251
1048 M   S   L   P   K   S   T   S   T   G   L   G   E   A   L   G   P   A   S   R  1067

3252 CGC ACC AGC AGC AGC GGG TCG GCA GAG CCT GGG GCG GCC CAC GAG ATG AAG TCA CCG CCC 3311
1068 R   T   S   S   S   G   S   A   E   P   G   A   A   H   E   M   K   S   P   P  1087

3312 AGC GCC CGC AGC TCT CCG CAC AGC CCC TGG AGC GCT GCA AGC AGC TGG ACC AGC AGG CGC 3371
1088 S   A   R   S   S   P   H   S   P   W   S   A   A   S   S   W   T   S   R   R  1107

3372 TCC AGC CGG AAC AGC CTC GGC CGT GCA CCC AGC CTG AAG CGG AGA AGC CCA AGT GGA GAG 3431
1108 S   S   R   N   S   L   G   R   A   P   S   L   K   R   R   S   P   S   G   E  1127

3432 CGG CGG TCC CTG TTG TCG GGA GAA GGC CAG GAG AGC CAG GAT GAA GAG GAG AGC TCA GAA 3491
1128 R   R   S   L   L   S   G   E   G   Q   E   S   Q   D   E   E   E   S   S   E  1147

3492 GAG GAG CGG GCC AGC CCT GCG GGC AGT GAC CAT CGC CAC AGG GGG TCC CTG GAG CGG GAG 3551
1148 E   E   R   A   S   P   A   G   S   D   H   R   H   R   G   S   L   E   R   E  1167

3552 GCC AAG AGT TCC TTT GAC CTG CCA GAC ACA CTG CAG GTG CCA GGG CTG CAT CGC ACT GCC 3611
1168 A   K   S   S   F   D   L   P   D   T   L   Q   V   P   G   L   H   R   T   A  1187

3612 AGT GGC CGA GGG TCT GCT TCT GAG CAC CAG GAC TGC AAT GGC AAG TCG GCT TCA GGG CGC 3671
1188 S   G   R   G   S   A   S   E   H   Q   D   C   N   G   K   S   A   S   G   R  1207

3672 CTG GCC CGG GCC CTG CGG CCT GAT GAC CCC CCA CTG GAT GGG GAT GAC GCC GAT GAC GAG 3731
1208 L   A   R   A   L   R   P   D   D   P   P   L   D   G   D   D   A   D   D   E  1227

3732 GGC AAC CTG AGC AAA GGG GAA CGG GTC CGC GCG TGG ATC CGA GCC CGA CTC CCT GCC TGC 3791
1228 G   N   L   S   K   G   E   R   V   R   A   W   I   R   A   R   L   P   A   C  1247

3792 TAC CTC GAG CGA GAC TCC TGG TCA GCC TAC ATC TTC CCT CCT CAG TCC AGG TTC CGC CTC 3851
1248 Y   L   E   R   D   S   W   S   A   Y   I   F   P   P   Q   S   R   F   R   L  1267

3852 CTG TGT CAC CGG ATC ATC ACC CAC AAG ATG TTC GAC CAC GTG GTC CTT GTC ATC ATC TTC 3911
1268 L   C   H   R   I   I   T   H   K   M   F   D   H   V   V   L   V   I   I   F  1287

3912 CTT AAC TGC ATC ACC ATC GCC ATG GAG CGC CCC AAA ATT GAC CCC CAC AGC GCT GAA CGC 3971
1288 L   N   C   I   T   I   A   M   E   R   P   K   I   D   P   H   S   A   E   R  1307

3972 ATC TTC CTG ACC CTC TCC AAT TAC ATC TTC ACC GCA GTC TTT CTG GCT GAA ATG ACA GTG 4031
1308 I   F   L   T   L   S   N   Y   I   F   T   A   V   F   L   A   E   M   T   V  1327

4032 AAG GTG GTG GCA CTG GGC TGG TGC TTC GGG GAG CAG GCG TAC CTG CGG AGC AGT TGG AAC 4091
1328 K   V   V   A   L   G   W   C   F   G   E   Q   A   Y   L   R   S   S   W   N  1347

4092 GTG CTG GAC GGG CTG TTG GTG CTC ATC TCC GTC ATC GAC ATT CTG GTG TCC ATG GTC TCT 4151
1348 V   L   D   G   L   L   V   L   I   S   V   I   D   I   L   V   S   M   V   S  1367

4152 GAC AGC GGC ACC AAG ATC CTG GGC ATG CTG AGG GTG CTG CGG CTG CTG CGG ACC CTG CGC 4211
1368 D   S   G   T   K   I   L   G   M   L   R   V   L   R   L   L   R   T   L   R  1387

4212 CCG CTC AGG GTG ATC AGC CGG GCG CAG GGG CTG AAG CTG GTG GTG GAG ACG CTG ATG TCC 4271
1388 P   L   R   V   I   S   R   A   Q   G   L   K   L   V   V   E   T   L   M   S  1407

4272 TCA CTG AAA CCC ATC GGC AAC ATT GTA GTC ATC TGC TGT GCC TTC TTC ATC ATT TTC GGC 4331
1408 S   L   K   P   I   G   N   I   V   V   I   C   C   A   F   F   I   I   F   G  1427

4332 ATC TTG GGG GTG CAG CTC TTC AAA GGG AAG TTT TTC GTG TGC CAG GGC GAG GAT ACC AGG 4391
1428 I   L   G   V   Q   L   F   K   G   K   F   F   V   C   Q   G   E   D   T   R  1447

4392 AAC ATC ACC AAT AAA TCG GAC TGT GCC GAG GCC AGT TAC CGG TGG GTC CGG CAC AAG TAC 4451
1448 N   I   T   N   K   S   D   C   A   E   A   S   Y   R   W   V   R   H   K   Y  1467
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4452 AAC TTT GAC AAC CTT GGC CAG GCC CTG ATG TCC CTG TTC GTT TTG GCC TCC AAG GAT GGT 4511
1468 N   F   D   N   L   G   Q   A   L   M   S   L   F   V   L   A   S   K   D   G 1487

4512 TGG GTG GAC ATC ATG TAC GAT GGG CTG GAT GCT GTG GGC GTG GAC CAG CAG CCC ATC ATG 4571
1488 W   V   D   I   M   Y   D   G   L   D   A   V   G   V   D   Q   Q   P   I   M 1507

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1508 N   H   N   P   W   M   L   L   Y   F   I   S   F   L   L   I   V   A   F   F 1527

4632 GTC CTG AAC ATG TTT GTG GGT GTG GTG GTG GAG AAC TTC CAC AAG TGT AGG CAG CAC CAG 4691
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1548 E   E   E   E   A   R   R   R   E   E   K   R   L   R   R   L   E   K   K   R 1567

4752 AGG AAA GCC CAG TGC AAA CCT TAC TAC TCC GAC TAC TCC CGC TTC CGG CTC CTC GTC CAC 4811
1568 R   K   A   Q   C   K   P   Y   Y   S   D   Y   S   R   F   R   L   L   V   H 1587

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1628 C   N   Y   I   F   T   V   I   F   V   L   E   S   V   F   K   L   V   A   F 1647

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1648 G   F   R   R   F   F   Q   D   R   W   N   Q   L   D   L   A   I   V   L   L 1667

5052 TCC ATC ATG GGC ATC ACG CTG GAG GAA ATC GAG GTC AAC GCC TCG CTG CCC ATC AAC CCC 5111
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1688 T   I   I   R   I   M   R   V   L   R   I   A   R   V   L   K   L   L   K   M 1707

5172 GCT GTG GGC ATG CGG GCG CTG CTG GAC ACG GTG ATG CAG GCC CTG CCC CAG GTG GGG AAC 5231
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1748 G   D   L   E   C   D   E   T   H   P   C   E   G   L   G   R   H   A   T   F 1767

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5892 ACT GCC GAG GGG CCC CTG GGA CAC AGG GGC TGG GGG CTC CCC AAA GCT CAG TCA GGC TCC 5951
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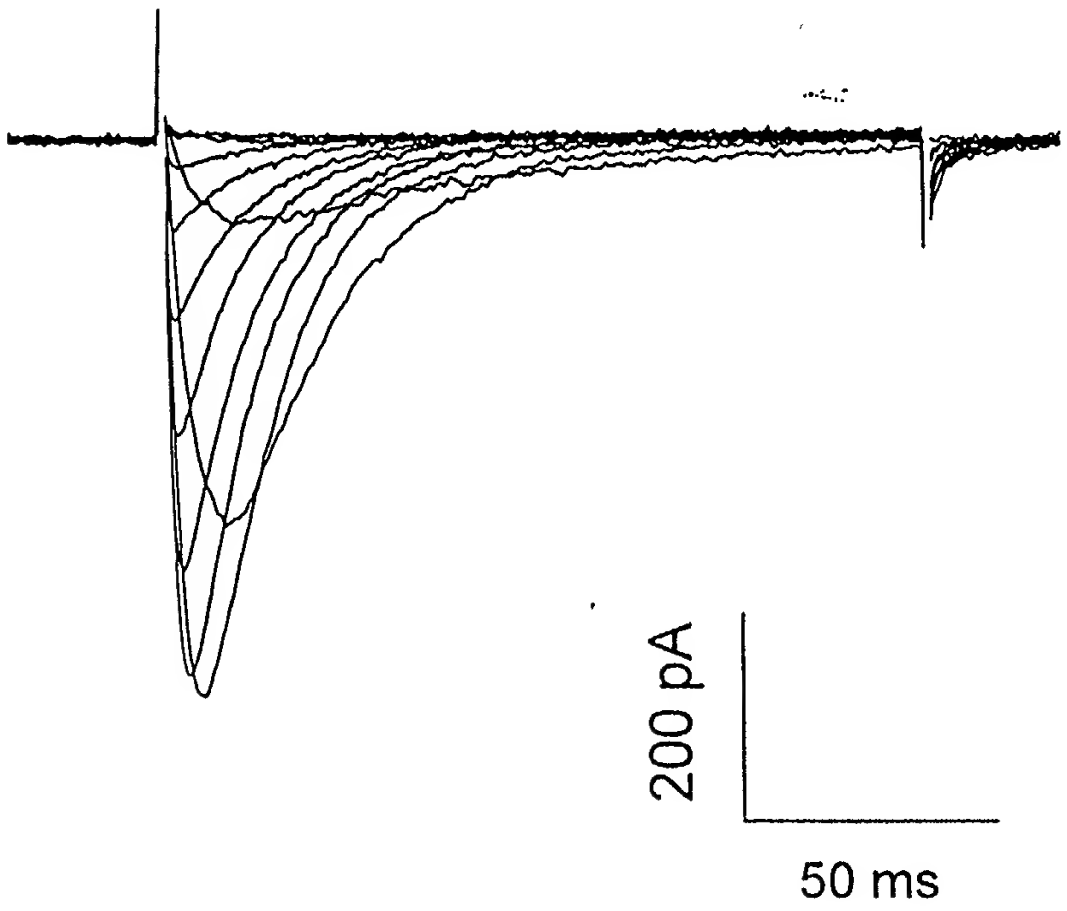

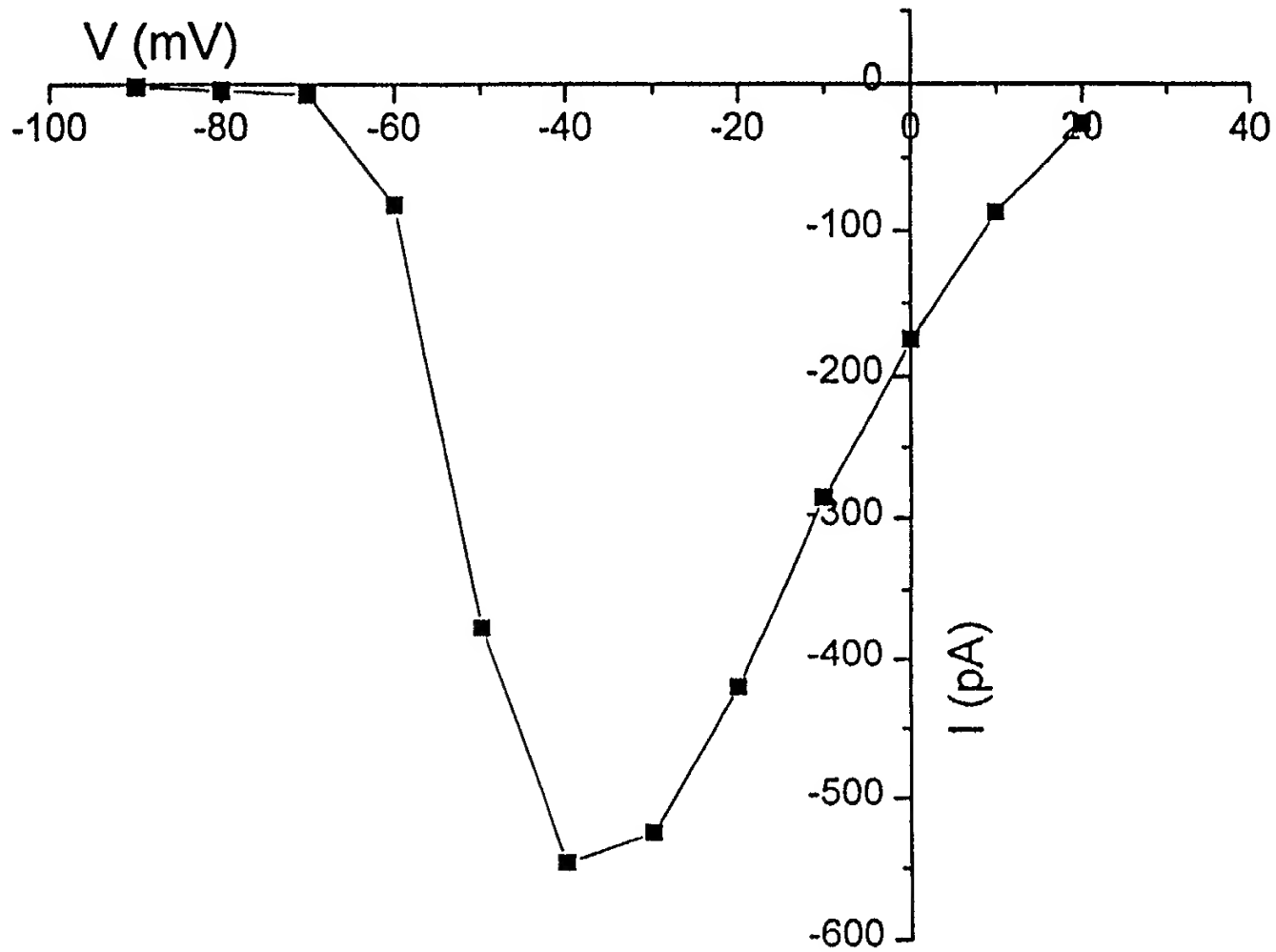

Figure 7

COMPARISON OF P-REGIONS

I	II	III	IV	
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LAASQ **E** GWVYV	QIITQ **E** GWTDV	ETLSY **K** GWNVV	RSVTG **E** DWNDI	NIC-2 (C27F2.3)
EASSQ **E** GWVFL	QILTQ **E** GWVDV	EVLSL **K** GWVEV	RIVTG **E** DWNKI	Rat-NIC
QCITM **E** GWTDV	QILTG **E** DWNSV	TVSTF **E** GWPEL	RCATG **E** AWQDI	L-Type Ca Channel
QVITL **E** GWVDI	QILTQ **E** DWNKV	VLASK **D** GWVDI	RVSTG **D** NWNGI	T-Type Ca Channel
RLMTQ **D** FWENL	RVLCG **E** WIETM	QVATF **K** GWMDI	QITTS **A** GWDGL	Na Channels

Fig. 8

SEQUENCE LISTING

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Baillie, David L.

<120> NOVEL HUMAN CALCIUM CHANNELS AND RELATED PROBES, CELL LINES AND METHODS

<130> NMED.P-001-2(CIP)

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<210> 18
<211> 1854
<212> PRT
<213> HUMAN

<220>
<223> human alpha-I partial sequence from BAC bK206c7

<400> 18

Met Phe Phe Val Ser Ala Asn Pro Trp Val Ser Phe Thr Ser Phe Asp
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Leu Asn Val Ala Asn Met Asp Asn Phe Phe Ala Pro Val Phe Thr Met
20 25 30

Gly Lys Tyr Tyr Thr Gln Gly Asp Lys Val Leu Met Pro Leu Ala Ile

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          35                  40                  45

Gln Ala Leu Lys Gln Leu Met Phe Lys Leu Val Ala Thr Val Ala Arg
     50                  55                  60

Thr His Ala Thr Pro Ser His Ile Thr Gly Gly Pro Gly Thr Gly Met
 65                  70                  75                  80

His Thr Gly Thr Phe Gln Glu Gly Ala Glu Pro Gly Ser Ser Gln His
                 85                  90                  95

Pro Glu Ala Gln Ala Thr Tyr Thr Ala Gly Cys Thr Pro Ala Pro Thr
            100                 105                 110

Gly Asp Pro Thr Cys Cys Phe Val Leu Asp Leu Val Cys Thr Trp Phe
        115                 120                 125

Glu Cys Val Ser Met Leu Val Ile Leu Leu Asn Cys Val Thr Leu Gly
    130                 135                 140

Met Tyr Gln Pro Cys Asp Asp Met Asp Cys Leu Ser Asp Arg Cys Lys
145                 150                 155                 160

Ile Leu Gln Val Phe Asp Asp Phe Ile Phe Ile Phe Phe Ala Met Glu
                165                 170                 175

Met Val Leu Lys Met Val Ala Leu Gly Ile Phe Gly Lys Lys Cys Tyr
            180                 185                 190

Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val Met Ala Gly
        195                 200                 205

Asn Ile Asn Leu Ser Ala Ile Arg Thr Val Arg Val Leu Arg Pro Leu
    210                 215                 220

Lys Ala Ile Asn Arg Val Pro Ser Met Arg Ile Leu Val Asn Leu Leu
225                 230                 235                 240

Leu Asp Thr Leu Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe
                245                 250                 255

Val Phe Phe Ile Phe Gly Ile Ile Gly Val Gln Leu Trp Ala Gly Leu
            260                 265                 270

Leu Arg Asn Arg Cys Phe Leu Glu Glu Asn Phe Thr Ile Gln Gly Asp
        275                 280                 285

Val Ala Leu Pro Pro Tyr Tyr Gln Pro Glu Glu Asp Asp Glu Met Pro
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    290                 295                 300

Phe Ile Cys Ser Leu Ser Gly Asp Asn Gly Ile Met Gly Cys His Glu
305                 310                 315                 320

Ile Pro Pro Leu Lys Glu Gln Gly Arg Glu Cys Cys Leu Ser Lys Asp
                325                 330                 335

Asp Val Tyr Asp Phe Gly Ala Gly Arg Gln Asp Leu Asn Ala Ser Gly
            340                 345                 350

Leu Cys Val Asn Trp Asn Arg Tyr Tyr Asn Val Cys Arg Thr Gly Ser
        355                 360                 365

Ala Asn Pro His Lys Gly Ala Ile Asn Phe Asp Asn Ile Gly Tyr Ala
    370                 375                 380

Trp Ile Val Ile Phe Gln Val Ile Thr Leu Glu Gly Trp Val Glu Ile
385                 390                 395                 400

Met Tyr Tyr Val Met Asp Ala His Ser Phe Tyr Asn Phe Ile Tyr Phe
                405                 410                 415

Ile Leu Leu Ile Ile Ser Glu Leu Ile His Leu Val Met Pro Asp Cys
            420                 425                 430

Ser Phe Ser Thr Ala Gln Ser Pro Lys Cys Gln Gly Asp Ser Leu Pro
        435                 440                 445

Gly Val Ala Ala Glu Ser Leu Leu Leu Arg Asp Ser Ser Ser Ser Val
    450                 455                 460

Ile Thr Asp Glu Ala Ala Ala Met Glu Asn Leu Leu Ala Gly Thr Ser
465                 470                 475                 480

Lys Gly Asp Glu Ser Tyr Leu Leu Arg Leu Ala Gly Ser Gln Val His
                485                 490                 495

Ser Gln Ala Gln Gln Met Leu Gly Arg Gly Leu Gly Pro Glu Ser Leu
            500                 505                 510

Glu Thr Gly Glu Glu Pro His Ser Trp Ser Pro Arg Ala Thr Arg Arg
        515                 520                 525

Trp Asp Pro Gln Cys Gln Pro Gly Gln Pro Leu Pro Leu His Phe Met
    530                 535                 540

Gln Ala Gln Val Gly Ser Phe Phe Met Ile Asn Leu Cys Leu Val Val
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545 550 555 560

Ile Ala Thr Gln Phe Ser Glu Thr Lys Gln Arg Glu His Arg Leu Met
565 570 575

Leu Glu Gln Arg Gln Arg Tyr Leu Ser Ser Ser Thr Val Ala Ser Tyr
580 585 590

Ala Glu Pro Gly Asp Cys Tyr Glu Glu Ile Phe Gln Tyr Val Cys His
595 600 605

Ile Leu Arg Lys Ala Lys Arg Arg Ala Leu Gly Leu Tyr Gln Ala Leu
610 615 620

Gln Ser Arg Arg Gln Ala Leu Gly Pro Glu Ala Pro Ala Pro Ala Lys
625 630 635 640

Pro Gly Pro His Ala Lys Glu Pro Arg His Tyr Pro Leu Thr Val Trp
645 650 655

Glu Ser Ile Leu Gly Arg Gln Ala Glu Glu Cys Thr Leu Arg Ala Ala
660 665 670

Ala His Pro Ser Ser Gly Ala Ser His Pro Gly Val Gly Ser Glu Glu
675 680 685

Ala Pro Glu Leu Cys Pro Gln His Ser Pro Leu Asp Ala Thr Pro His
690 695 700

Thr Leu Val Gln Pro Ile Pro Ala Thr Leu Ala Ser Asp Pro Ala Ser
705 710 715 720

Cys Pro Cys Cys Gln His Glu Asp Gly Arg Arg Pro Ser Gly Leu Gly
725 730 735

Ser Thr Asp Ser Gly Gln Glu Gly Ser Gly Ser Gly Ser Ser Ala Gly
740 745 750

Gly Glu Asp Glu Ala Asp Gly Asp Gly Ala Arg Ser Ser Glu Asp Gly
755 760 765

Ala Ser Ser Glu Leu Gly Lys Glu Glu Glu Glu Glu Glu Gln Ala Asp
770 775 780

Gly Ala Val Trp Leu Cys Gly Asp Val Trp Arg Glu Thr Arg Ala Lys
785 790 795 800

Leu Arg Gly Ile Val Asp Ser Lys Tyr Phe Asn Arg Gly Ile Met Met

805 810 815

Ala Ile Leu Val Asn Thr Val Ser Met Gly Ile Glu His His Glu Gln
820 825 830

Ala Ser Ala Ala Gln Pro Gly Arg Ala Cys Gly Arg Gly Gln Asn Pro
835 840 845

Asp Leu Cys Met Thr Leu Lys Ala Pro Cys Leu Cys His Asn Val Pro
850 855 860

Ser Pro Gly Gln Gly Val Leu Ser His Pro Val Thr Pro Pro His Thr
865 870 875 880

Ala Pro Trp Arg Met Glu Thr Gly Lys Gln Gly His Gly Cys Glu Glu
885 890 895

Gly Pro Gly Gln Arg Ser Ser Asp Met Phe Ala Leu Glu Met Ile Leu
900 905 910

Lys Leu Ala Ala Phe Gly Leu Phe Asp Tyr Leu Arg Asn Pro Tyr Asn
915 920 925

Ile Phe Asp Ser Ile Ile Val Ile Ile Ser Ile Trp Glu Ile Val Gly
930 935 940

Gln Ala Asp Gly Gly Leu Ser Val Leu Arg Thr Phe Arg Leu Leu Arg
945 950 955 960

Val Leu Lys Leu Val Arg Phe Met Pro Ala Leu Arg Arg Gln Leu Val
965 970 975

Val Leu Met Lys Thr Met Asp Asn Val Ala Thr Phe Cys Met Leu Leu
980 985 990

Met Leu Phe Ile Phe Ile Phe Ser Ile Leu Gly Met His Ile Phe Gly
995 1000 1005

Cys Lys Phe Ser Leu Arg Thr Asp Thr Gly Asp Thr Val Pro Asp Arg
1010 1015 1020

Lys Asn Phe Asp Ser Leu Leu Trp Ala Ile Val Thr Val Phe Gln Ile
1025 1030 1035 1040

Leu Thr Gln Glu Asp Trp Asn Val Val Leu Tyr Asn Gly Met Ala Ser
1045 1050 1055

Thr Ser Pro Trp Ala Ser Leu Tyr Phe Val Ala Leu Met Thr Phe Gly

1060 1065 1070

Asn Tyr Val Leu Phe Asn Leu Leu Val Ala Ile Leu Val Glu Gly Phe
1075 1080 1085

Gln Ala Glu Val Thr Val Val Leu Ala Glu Glu Ala Pro Pro Gln Gly
1090 1095 1100

Leu Arg Lys Thr Gly Arg Gly Arg Gly Gly Leu Asp Gly Gly Gly Leu
1105 1110 1115 1120

Gln Phe Lys Leu Leu Ala Gly Asn Leu Ser Leu Lys Glu Gly Val Ala
1125 1130 1135

Asp Glu Val Gly Asp Ala Asn Arg Ser Tyr Ser Asp Glu Asp Gln Ser
1140 1145 1150

Ser Ser Asn Ile Glu Glu Phe Asp Lys Leu Gln Glu Gly Leu Asp Ser
1155 1160 1165

Ser Gly Asp Pro Lys Leu Cys Pro Ile Pro Met Thr Pro Asn Gly His
1170 1175 1180

Leu Asp Pro Ser Leu Pro Leu Gly Gly His Leu Gly Pro Ala Gly Ala
1185 1190 1195 1200

Ala Gly Pro Ala Pro Arg Leu Ser Leu Gln Pro Asp Pro Met Leu Val
1205 1210 1215

Ala Leu Gly Ser Arg Lys Ser Ser Val Met Ser Leu Gly Arg Met Ser
1220 1225 1230

Tyr Asp Gln Arg Ser Leu Val Gly Gly Leu Arg Ala Thr Ala Gly Val
1235 1240 1245

Gln Ala Ala Phe Gly His Leu Val Pro Gln Pro Trp Val Cys Leu Trp
1250 1255 1260

Gly Ala Asp Pro Asn Gly Asn Ser Phe Gln Ser Ser Ser Arg Ser Ser
1265 1270 1275 1280

Tyr Tyr Gly Pro Trp Gly Arg Ser Ala Ala Trp Ala Ser Arg Arg Ser
1285 1290 1295

Ser Trp Asn Ser Leu Lys His Lys Pro Pro Ser Ala Glu His Glu Ser
1300 1305 1310

Leu Leu Ser Ala Glu Arg Gly Gly Gly Ala Arg Val Cys Glu Val Ala

1315 1320 1325

Ala Asp Glu Gly Pro Pro Arg Ala Ala Pro Leu His Thr Pro His Ala
1330 1335 1340

His His Val His His Gly Pro His Leu Ala His Arg His Arg His His
1345 1350 1355 1360

Arg Arg Thr Leu Ser Leu Asp Asn Arg Asp Ser Val Asp Leu Ala Glu
1365 1370 1375

Leu Val Pro Ala Val Gly Ala His Pro Arg Ala Ala Trp Arg Ala Ala
1380 1385 1390

Gly Pro Ala Pro Gly His Glu Asp Cys Asn Gly Arg Met Pro Ser Ile
1395 1400 1405

Ala Lys Asp Val Phe Thr Lys Met Gly Asp Arg Gly Asp Arg Gly Glu
1410 1415 1420

Asp Glu Glu Glu Ile Asp Tyr Val Ser Gly Gly Gly Ala Glu Gly Asp
1425 1430 1435 1440

Leu Thr Leu Cys Phe Arg Val Arg Lys Met Ile Asp Val Tyr Lys Pro
1445 1450 1455

Asp Trp Cys Glu Val Arg Glu Asp Trp Ser Val Tyr Leu Phe Ser Pro
1460 1465 1470

Glu Asn Arg Leu Arg Asp Leu Gly Trp Val Ser Leu Glu Cys Gln Gly
1475 1480 1485

Lys Val Gly Asp Leu Val Val Trp Val Tyr Gly Gln Arg Arg Gln Arg
1490 1495 1500

Gln Thr Ile Ile Ala His Lys Leu Phe Asp Tyr Val Val Leu Ala Phe
1505 1510 1515 1520

Ile Phe Leu Asn Cys Ile Thr Ile Ala Leu Glu Arg Pro Gln Ile Glu
1525 1530 1535

Ala Gly Ser Thr Glu Arg Ile Phe Leu Thr Val Ser Asn Tyr Ile Phe
1540 1545 1550

Thr Ala Ile Phe Val Gly Glu Met Thr Leu Lys Val Val Ser Leu Gly
1555 1560 1565

Leu Tyr Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu

1570 1575 1580

Asp Gly Phe Leu Val Phe Val Ser Ile Ile Asp Ile Val Val Ser Leu
1585 1590 1595 1600

Ala Ser Ala Gly Gly Ala Lys Ile Leu Gly Val Leu Arg Val Leu Arg
1605 1610 1615

Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Pro Gly
1620 1625 1630

Leu Lys Leu Val Val Glu Thr Leu Ile Ser Ser Leu Lys Pro Ile Gly
1635 1640 1645

Asn Ile Val Leu Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu
1650 1655 1660

Gly Val Gln Leu Phe Lys Gly Lys Phe Tyr His Cys Leu Gly Val Asp
1665 1670 1675 1680

Thr Arg Asn Ile Thr Asn Arg Ser Asp Cys Met Ala Ala Asn Tyr Arg
1685 1690 1695

Trp Val His His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met
1700 1705 1710

Ser Leu Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asn Ile Met Tyr
1715 1720 1725

Asn Gly Leu Asp Ala Val Ala Val Asp Gln Gln Pro Val Thr Asn His
1730 1735 1740

Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ser
1745 1750 1755 1760

Phe Phe Val Leu Asn Met Phe Val Gly Val Val Val Glu Asn Phe His
1765 1770 1775

Lys Cys Arg Gln His Gln Glu Ala Glu Glu Ala Arg Arg Arg Glu Glu
1780 1785 1790

Lys Arg Leu Arg Arg Leu Glu Lys Lys Arg Arg Lys Ala Gln Arg Leu
1795 1800 1805

Pro Tyr Tyr Ala Thr Tyr Cys His Thr Arg Leu Leu Ile His Ser Met
1810 1815 1820

Cys Thr Ser His Tyr Leu Asp Ile Phe Ile Thr Phe Ile Ile Cys Leu

1825 1830 1835 1840

Asn Val Val Thr Met Ser Leu Glu His Tyr Asn Gln Pro Thr
1845 1850

<210> 19
<211> 567
<212> DNA
<213> HUMAN

<220>
<223> human alpha-I partial sequence

<400> 19
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ctgcgtaacc gctgcttcct ggaggagaac ttcaccatac aaggggatgt ggccttgccc 180
ccatactacc agccggagga ggatgatgag atgcccttca tctgctccct gtcgggcgac 240
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aagggtgcca tcagctttga caacatcggt tatgcttgga ttgtcatctt ccaggtgatc 480
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ttcgtctact tcatcctgct tatcata 567

<210> 20
<211> 189
<212> PRT
<213> HUMAN

<220>
<223> human alpha-I partial sequence

<400> 20
Met Arg Ile Leu Val Asn Leu Leu Leu Asp Thr Leu Pro Met Leu Gly
1 5 10 15

Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Thr Phe Gly Ile Ile
20 25 30

Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg Cys Phe Leu Glu
35 40 45

Glu Asn Phe Thr Ile Gln Gly Asp Val Ala Leu Pro Pro Tyr Tyr Gln
50 55 60

Pro Glu Glu Asp Asp Glu Met Pro Phe Ile Cys Ser Leu Ser Gly Asp

15

65 70 75 80

Asn Gly Ile Met Gly Cys His Glu Ile Pro Pro Leu Lys Glu Gln Gly
85 90 95

Arg Glu Cys Cys Leu Ser Lys Asp Asp Val Tyr Asp Phe Gly Ala Gly
100 105 110

Arg Gln Asp Leu Asn Ala Ser Gly Leu Cys Val Asn Trp Asn Arg Tyr
115 120 125

Tyr Asn Val Cys Arg Thr Gly Ser Ala Asn Pro His Lys Gly Ala Ile
130 135 140

Ser Phe Asp Asn Ile Gly Tyr Ala Trp Ile Val Ile Phe Gln Val Ile
145 150 155 160

Thr Leu Glu Gly Trp Val Ala Ile Met Tyr Tyr Val Met Asp Ala Leu
165 170 175

Ser Phe Tyr Asn Phe Val Tyr Phe Ile Leu Leu Ile Ile
180 185

<210> 21
<211> 567
<212> DNA
<213> rat

<220>
<223> rat alpha-I partial sequence

<400> 21
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ctacggaacc gctgcttcct ggaagaaaac ttcaccatac aaggggatgt ggccctgccc 180
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<210> 22
<211> 189
<212> PRT
<213> rat

<220>
<223> rat alpha-I partial sequence

<400> 22

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Met Arg Ile Leu Val Asn Leu Leu Leu Asp Thr Leu Pro Met Leu Gly
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Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Ile Phe Gly Ile Ile
             20                  25                  30

Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg Cys Phe Leu Glu
         35                  40                  45

Glu Asn Phe Thr Ile Gln Gly Asp Val Ala Leu Pro Pro Tyr Tyr Gln
     50                  55                  60

Pro Glu Glu Asp Asp Glu Met Pro Phe Ile Cys Ser Leu Thr Gly Asp
 65                  70                  75                  80

Asn Gly Ile Met Gly Cys His Glu Ile Pro Pro Leu Lys Glu Gln Gly
                 85                  90                  95

Arg Glu Cys Cys Leu Ser Lys Asp Asp Val Tyr Asp Phe Gly Ala Gly
            100                 105                 110

Arg Gln Asp Leu Asn Ala Ser Gly Leu Cys Val Asn Trp Asn Arg Tyr
        115                 120                 125

Tyr Asn Val Cys Arg Thr Gly Asn Ala Asn Pro His Lys Gly Ala Ile
    130                 135                 140

Asn Phe Asp Asn Ile Gly Tyr Ala Trp Ile Val Ile Phe Gln Val Ile
145                 150                 155                 160

Thr Leu Glu Gly Trp Val Glu Ile Met Tyr Tyr Val Met Asp Ala His
                165                 170                 175

Ser Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile
            180                 185
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<210> 23
<211> 7540
<212> DNA
<213> rat

<400> 23

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tgccaggcgc cccctcccag gtccccatct gaggcatccg gcaggactgt gggcagcggg 2040
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gtagaggtgg ctgccagctc tgggccccca accctcacca gcctcaacat cccacccggg 2160
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<210> 31
<211> 644
<212> PRT
<213> HUMAN

<400> 31
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1 5 10 15

Arg Ser Phe Met Arg Leu Asn Asp Leu Ser Gly Ala Gly Gly Arg Pro
20 25 30

Gly Pro Gly Ser Ala Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala
35 40 45

Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu
50 55 60

Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn
65 70 75 80

Pro Trp Phe Glu Arg Ile Ser Met Leu Val Ile Leu Leu Asn Cys Val
85 90 95

Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln
100 105 110

Arg Cys Arg Ile Leu Gln Ala Phe Asp Asp Phe Ile Phe Ala Phe Phe
115 120 125

Ala Val Glu Met Val Val Lys Met Val Ala Leu Gly Ile Phe Gly Lys
130 135 140

Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val
145 150 155 160

Ile Ala Gly Met Leu Glu Tyr Ser Leu Asp Leu Gln Asn Val Ser Phe
165 170 175

Ser Ala Val Arg Thr Val Arg Val Leu Arg Pro Leu Arg Ala Ile Asn
180 185 190

Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu Asp Thr Leu
195 200 205

Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Ile
210 215 220

Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg
225 230 235 240

Cys Phe Leu Pro Glu Asn Phe Ser Leu Pro Leu Ser Val Asp Leu Glu
245 250 255

Arg Tyr Tyr Gln Thr Glu Asn Glu Asp Glu Ser Pro Phe Ile Cys Ser
260 265 270

Gln Pro Arg Glu Asn Gly Met Arg Ser Cys Arg Ser Val Pro Thr Leu
275 280 285

Arg Gly Asp Gly Gly Gly Gly Pro Pro Cys Gly Leu Asp Tyr Glu Ala
290 295 300

Tyr Asn Ser Ser Ser Asn Thr Thr Cys Val Asn Trp Asn Gln Tyr Tyr
305 310 315 320

Thr Asn Cys Ser Ala Gly Glu His Asn Pro Phe Lys Gly Ala Ile Asn
325 330 335

Phe Asp Asn Ile Gly Tyr Ala Trp Ile Ala Ile Phe Gln Val Ile Thr
340 345 350

Leu Glu Gly Trp Val Asp Ile Met Tyr Phe Val Met Asp Ala His Ser
355 360 365

Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile Val Gly Ser Phe
370 375 380

Phe Met Ile Asn Leu Cys Leu Val Val Ile Ala Thr Gln Phe Ser Glu
385 390 395 400

Thr Lys Gln Arg Glu Ser Gln Leu Met Arg Glu Gln Arg Val Arg Phe
405 410 415

Leu Ser Asn Ala Ser Thr Leu Ala Ser Phe Ser Glu Pro Gly Ser Cys
420 425 430

Tyr Glu Glu Leu Leu Lys Tyr Leu Val Tyr Ile Leu Arg Lys Ala Ala
435 440 445

Arg Arg Leu Ala Gln Val Ser Arg Ala Ala Gly Val Arg Val Gly Leu
450 455 460

Leu Ser Ser Pro Ala Pro Leu Gly Gly Gln Glu Thr Gln Pro Ser Ser
465 470 475 480

Ser Cys Ser Arg Ser His Arg Arg Leu Ser Val His His Leu Val His
485 490 495

His His His His His His His His Tyr His Leu Gly Asn Gly Thr Leu
500 505 510

Arg Ala Pro Arg Ala Ser Pro Glu Ile Gln Asp Arg Asp Ala Asn Gly
515 520 525

Ser Arg Arg Leu Met Leu Pro Pro Pro Ser Thr Pro Ala Leu Ser Gly
530 535 540

Ala Pro Pro Gly Gly Ala Glu Ser Val His Ser Phe Tyr His Ala Asp
545 550 555 560

Cys His Leu Glu Pro Val Arg Cys Gln Ala Pro Pro Pro Arg Ser Pro
565 570 575

Ser Glu Ala Ser Gly Arg Thr Val Gly Ser Gly Lys Val Tyr Pro Thr
580 585 590

Val His Thr Ser Pro Pro Pro Glu Thr Leu Lys Glu Lys Ala Leu Val
595 600 605

Glu Val Ala Ala Ser Ser Gly Pro Pro Thr Leu Thr Ser Leu Asn Ile
610 615 620

Pro Pro Gly Pro Tyr Ser Ser Met His Lys Leu Leu Glu Thr Gln Ser
625 630 635 640

Thr Gly Ala Cys

<210> 32
<211> 1608
<212> DNA
<213> HUMAN

<400> 32
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cggcgttggt gggggcgtcc ccggagagcc ccggggcgcc gggacgcgag gcggagcggg 180
ggtccgagct cggcgtgtca ccctccgaga gcccggcggc cgagcgcggc gcggagctgg 240
gtgccgacga ggagcagcgc gtcccgtacc cggccttggc ggccacggtc ttcttctgcc 300
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gtgaggacgt tgagtgcggc tccgagcgct gcaacatcct ggaggccttt gacgccttca 480
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agagccgctg gcgcaagaag gtggacccca gtgctgtgca aggccagggt cccgggcacc 1560
gccagcgccg ggcaggcagg cacacagcct cggtgcacca cctggtct 1608

<210> 33
<211> 518
<212> PRT
<213> HUMAN

<400> 33
Met Thr Glu Gly Ala Arg Ala Ala Asp Glu Val Arg Val Pro Leu Gly
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Ala Pro Pro Pro Gly Pro Ala Ala Leu Val Gly Ala Ser Pro Glu Ser
20 25 30

Pro Gly Ala Pro Gly Arg Glu Ala Glu Arg Gly Ser Glu Leu Gly Val
35 40 45

Ser Pro Ser Glu Ser Pro Ala Ala Glu Arg Gly Ala Glu Leu Gly Ala
50 55 60

Asp Glu Glu Gln Arg Val Pro Tyr Pro Ala Leu Ala Ala Thr Val Phe
65 70 75 80

Phe Cys Leu Gly Gln Thr Thr Arg Pro Arg Ser Trp Cys Leu Arg Leu
85 90 95

Val Cys Asn Pro Trp Phe Glu His Val Ser Met Leu Val Ile Met Leu
100 105 110

Asn Cys Val Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Val Glu Cys
115 120 125

Gly Ser Glu Arg Cys Asn Ile Leu Glu Ala Phe Asp Ala Phe Ile Phe
130 135 140

Ala Phe Phe Ala Val Glu Met Val Ile Lys Met Val Ala Leu Gly Leu
145 150 155 160

Phe Gly Gln Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe

165 170 175

Phe Ile Val Val Ala Gly Met Met Glu Tyr Ser Leu Asp Gly His Asn
180 185 190

Val Ser Leu Ser Ala Ile Arg Thr Val Arg Val Leu Arg Pro Leu Arg
195 200 205

Ala Ile Asn Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu
210 215 220

Asp Thr Leu Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val
225 230 235 240

Phe Phe Ile Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu
245 250 255

Arg Asn Arg Cys Phe Leu Asp Ser Ala Phe Val Arg Asn Asn Asn Leu
260 265 270

Thr Phe Leu Arg Pro Tyr Tyr Gln Thr Glu Glu Gly Glu Glu Asn Pro
275 280 285

Phe Ile Cys Ser Ser Arg Arg Asp Asn Gly Met Gln Lys Cys Ser His
290 295 300

Ile Pro Gly Arg Arg Glu Leu Arg Met Pro Cys Thr Leu Gly Trp Glu
305 310 315 320

Ala Tyr Thr Gln Pro Gln Ala Glu Gly Val Gly Ala Ala Arg Asn Ala
325 330 335

Cys Ile Asn Trp Asn Gln Tyr Tyr Asn Val Cys Arg Ser Gly Asp Ser
340 345 350

Asn Pro His Asn Gly Ala Ile Asn Phe Asp Asn Ile Gly Tyr Ala Trp
355 360 365

Ile Ala Ile Phe Gln Val Ile Thr Leu Glu Gly Trp Val Asp Ile Met
370 375 380

Tyr Tyr Val Met Asp Ala His Ser Phe Tyr Asn Phe Ile Tyr Phe Ile
385 390 395 400

Leu Leu Ile Ile Val Gly Ser Phe Phe Met Ile Asn Leu Cys Leu Val
405 410 415

Val Ile Ala Thr Gln Phe Ser Glu Thr Lys Gln Arg Glu Ser Gln Leu

420 425 430

Met Arg Glu Gln Arg Ala Arg His Leu Ser Asn Asp Ser Thr Leu Ala
435 440 445

Ser Phe Ser Glu Pro Gly Ser Cys Tyr Glu Glu Leu Leu Lys Tyr Val
450 455 460

Gly His Ile Phe Arg Lys Val Lys Arg Arg Ser Leu Arg Leu Tyr Ala
465 470 475 480

Arg Trp Gln Ser Arg Trp Arg Lys Lys Val Asp Pro Ser Ala Val Gln
485 490 495

Gly Gln Gly Pro Gly His Arg Gln Arg Arg Ala Gly Arg His Thr Ala
500 505 510

Ser Val His His Leu Val
515

<210> 34
<211> 1080
<212> DNA
<213> HUMAN

<400> 34
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acagcctcaa gcacaagccg ccgtcggcgg agcatgagtc cctgctctct gcggagcgcg 180
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tgcacacccc acacgcccac cacattcatc acgggcccca tctggcgcac cgccaccgcc 300
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ccgcggtggg cgcccacccc cgggccgcct ggagggcggc aggcccggcc cccgggcatg 420
aggactgcaa tggcaggatg cccagcatcg ccaaagacgt cttcaccaag atgggcgacc 480
gcggggatcg cggggaggat gaggaggaaa tcgactacac cctgtgcttc cgcgtccgca 540
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tcgactacgt cgtcctggcc ttcatctttc tcaactgcat caccatcgcc ctggagcggc 720
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cggccatctt cgtgggcgag atgacattga aggtagtctc gctgggcctg tacttcggcg 840
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tcatcgacat cgtggtgtcc ctggcctcag ccgggggagc caagatcttg gggtcctcc 960
gagtcttgcg gctcctgcgc accctacgcc ccctgcgtgt catcagccgg gcgccgggcc 1020
tgaagctggt ggtggagaca ctcatctcct ccctcaagcc catcggcaac atcgtgctca 1080

<210> 35
<211> 359

<212> PRT
<213> HUMAN

<400> 35

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Ser Val Met Ser Leu Gly Arg Met Ser Tyr Asp Gln Arg Ser Leu Ser
  1               5                  10                  15

Ser Ser Arg Ser Ser Tyr Tyr Gly Pro Trp Gly Arg Ser Ala Ala Trp
             20                  25                  30

Ala Ser Arg Arg Ser Ser Trp Asn Ser Leu Lys His Lys Pro Pro Ser
         35                  40                  45

Ala Glu His Glu Ser Leu Leu Ser Ala Glu Arg Gly Gly Gly Ala Arg
     50                  55                  60

Val Cys Glu Val Ala Ala Asp Glu Gly Pro Pro Arg Ala Ala Pro Leu
 65                  70                  75                  80

His Thr Pro His Ala His His Ile His His Gly Pro His Leu Ala His
                 85                  90                  95

Arg His Arg His His Arg Arg Thr Leu Ser Leu Asp Asn Arg Asp Ser
            100                 105                 110

Val Asp Leu Ala Glu Leu Val Pro Ala Val Gly Ala His Pro Arg Ala
        115                 120                 125

Ala Trp Arg Ala Ala Gly Pro Ala Pro Gly His Glu Asp Cys Asn Gly
    130                 135                 140

Arg Met Pro Ser Ile Ala Lys Asp Val Phe Thr Lys Met Gly Asp Arg
145                 150                 155                 160

Gly Asp Arg Gly Glu Asp Glu Glu Glu Ile Asp Tyr Thr Leu Cys Phe
                165                 170                 175

Arg Val Arg Lys Met Ile Asp Val Tyr Lys Pro Asp Trp Cys Glu Val
            180                 185                 190

Arg Glu Asp Trp Ser Val Tyr Leu Phe Ser Pro Glu Asn Arg Phe Arg
        195                 200                 205

Val Leu Cys Gln Thr Ile Ile Ala His Lys Leu Phe Asp Tyr Val Val
    210                 215                 220

Leu Ala Phe Ile Phe Leu Asn Cys Ile Thr Ile Ala Leu Glu Arg Pro
225                 230                 235                 240
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Gln Ile Glu Ala Gly Ser Thr Glu Arg Ile Phe Leu Thr Val Ser Asn
245 250 255

Tyr Ile Phe Thr Ala Ile Phe Val Gly Glu Met Thr Leu Lys Val Val
260 265 270

Ser Leu Gly Leu Tyr Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp
275 280 285

Asn Val Leu Asp Gly Phe Leu Val Phe Val Ser Ile Ile Asp Ile Val
290 295 300

Val Ser Leu Ala Ser Ala Gly Gly Ala Lys Ile Leu Gly Val Leu Arg
305 310 315 320

Val Leu Arg Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg
325 330 335

Ala Pro Gly Leu Lys Leu Val Val Glu Thr Leu Ile Ser Ser Leu Lys
340 345 350

Pro Ile Gly Asn Ile Val Leu
355